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Part I. An Investigation of the Acid-Catalyzed Alpha-Pyridilic Acid Rearrangement. Part II. The Chemistry of Mixed Aliphatic-Aromatic Tertiary Amides.

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PART I. AN INVESTIGATION OF THE ACID-CATALYZED ALPHA-PYRIDILIC ACID REARRANGEMENT. PART II. THE CHEMISTRY OF MIXED ALIPHATIC-AROMATIC TERTIARY AMIDES.

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ABSTRACT

I. AN INVESTIGATION OF THE ACID-CATALYZED ALPHA-PYRIDILIC ACID REARRANGEMENT.

Alpha-pyridil, when subjected to the usual conditions of base-catalyzed reaction, undergoes the benzilic acid rearrangement to form the unstable alpha-pyridilic acid salt, which spontaneously decarboxylates in solution to form alpha-dipyridyl carbinol. Until the present investigation, it was thought that rearrangement also occurred under hydrochloric acid catalysis, but through a different mechanism than that of the usual base-catalyzed rearrangement. This observed reaction was called the "alpha-pyridilic acid rearrangement," and the product was given the name "alpha-pyridilic acid dihydrochloride."

This paper describes an attempted characterization of "alpha-pyridilic acid dihydrochloride," in which several unsuccessful attempts were made to prepare typical carboxylic acid derivatives of the compound. It was observed that the compound did not react as a typical carboxylic acid. The acid-catalyzed reaction in which "alpha-pyridilic acid" was prepared was shown to be reversible--a phenomenon which was not predicted by the postulated rearrangement mechanism; and it was found that the compound in question could be prepared in the absence of water--an observation also contradictory to the suggested mechanism. Thus the present investigation proves that the so-called "alpha-pyridilic acid dihydrochloride" is actually alpha-pyridil dihydrochloride monohydrate.

II. THE CHEMISTRY OF MIXED ALIPHATIC-AROMATIC TERTIARY AMIDES.

An investigation of the chemical properties of mixed aliphatic-aromatic tertiary amides has been made, using N-acetyldibenzamide as a representative of this group. Synthesis of a previously-unknown tertiary amide, N-propionyldiacetamide, is reported. Preparations and reactions of acylpyridinium chlorides are discussed with relation to preparation of tertiary amides.

Isopropenyl acetate was caused to react with dipropionamide in an attempt to prepare N-acetyldipropionamide; instead, N-propionyldiacetamide was isolated. An explanation is offered for these results.

Benzoylpyridinium chloride was prepared in diethyl ether and allowed to react with dipropionamide; no acylated product was observed. No success was achieved with diacylation of formamide by benzoylpyridinium chloride. Methacryloylpyridinium chloride was prepared and allowed to react with benzamide in two different solvents and at three different temperatures; unreacted benzamide and methacrylic acid were recovered. Dibenzoylation, known to occur in chloroform at low temperatures, was attempted, using diethyl ether as solvent; no reaction took place.

N-Acetyldibenzamide was allowed to react with various nucleophilic agents. Hydrolysis yielded a mixture of benzamide, dibenzamide, and benzoic acid; ethanolysis gave benzamide and ethyl benzoate. Reaction with amines produced N-alkylbenzamides and N-alkylacetamides. N-Acetyldibenzamide with phenylhydrazine produced

benzoic acid phenylhydrazide. Hydrazinolysis of N-acetyldibenzamide occurred, resulting in the formation of diacetylhydrazine.

Other reactions included those with acid chlorides, in which the starting material was evidently not affected, pyrolysis to benzonitrile, reaction with sulfuric acid to form carboxylic acid, and bromination. Friedel-Crafts reaction of N-acetyldibenzamide produced acetophenone and dibenzamide.

Reduction of the compound gave N-benzylbenzamide and benzamide with zinc and acetic acid, and benzyl alcohol and benzamide from the sodium borohydride reduction. An attempted Clemmensen reduction produced only a brown oil.

On the basis of infrared and n.m.r. spectral studies, a pyramidal structure was assigned to tertiary amides.

I. AN INVESTIGATION OF THE ACID-CATALYZED ALPHA-PYRIDILIC ACID REARRANGEMENT

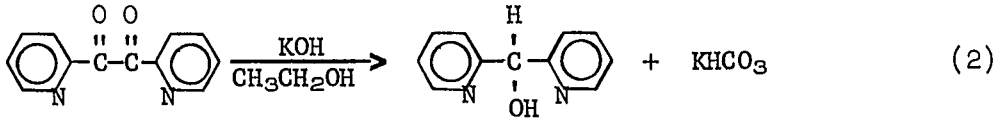
INTRODUCTION

The benzilic acid rearrangement derives its name from the product of the base-catalyzed rearrangement of benzil; the reaction was first observed by G. Shroeter in 1909.[1] The rearrangement may be formulated by the following equation.

$$C_6H_5\text{-}CO\text{-}CO\text{-}C_6H_5 + KOH \longrightarrow (C_6H_5)_2C(OH)\text{-}CO_2^-K^+ \qquad (1)$$

When benzil is treated with aqueous hydrochloric acid under reflux, no reaction occurs, and the starting material is recovered unchanged; thus the benzilic acid rearrangement occurs only in basic solution.

In 1962, Barakeh investigated the possibility of carrying out the base-catalyzed benzilic acid rearrangement on a diketone having alpha-pyridine rings instead of benzene rings on both sides of the dicarbonyl,[2] to discover whether one would obtain the alpha-pyridilic acid salt analogous to the benzilic acid salt shown in equation (1). Barakeh's work indicated that alpha-pyridil does in fact undergo rearrangement in basic solution to form the unstable salt which spontaneously decarboxylates in solution to form alpha-dipyridyl carbinol[2] according to equation (2). Barakeh also



$$+ \ KHCO_3 \qquad (2)$$

reported that alpha-pyridil, unlike benzil, rearranged under reflux with aqueous hydrochloric acid to form a previously unknown compound which he called "alpha-pyridilic acid dihydrochloride."[2]

The present paper reports various attempts to characterize "alpha-pyridilic acid dihydrochloride" by attempted preparations of carboxylic acid derivatives of the compound, none of which was successful. An independent preparation of "alpha-pyridilic acid dihydrochloride" in the absence of water is reported, as is also the reversibility of formation of the compound. Thus the identity of the compound in question is established as being the isomeric alpha-pyridil dihydrochloride monohydrate.

HISTORICAL PART

The benzilic acid rearrangement was first observed by G. Schroeter[1] in 1909. It is to be emphasized that the reaction, catalyzed by potassium hydroxide or potassium alkoxide,[3] involves not only molecular rearrangement but also addition of a molecule of water, or alcohol in the case of alkoxide catalysis.

In 1957 Klosa observed the first instance of what he described as "the long-sought pyridilic acid rearrangement" by modifying the conditions of the benzilic acid rearrangement and using sodium in methanol as the catalyst. He obtained the sodium salt of alpha-pyridilic acid in low yield and reported that the product was amphoteric; alpha-pyridilic acid itself was not isolated.[4]

Oda reacted alpha-pyridil with aqueous alkali in 1961 but reported only a small degree of rearrangement; however, he observed that 3,3'-pyridil rearranged readily, as did alpha-pyridil-N,N'-dioxide, to give good yields of rearranged product.[5]

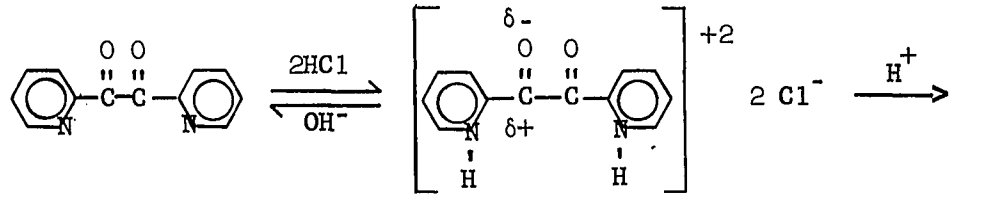
The most recent report of a pyridilic acid rearrangement came from St. Black, who observed a molecular rearrangement of the benzilic acid type promoted by metal chelation. He found that alpha-pyridil reacts with hydrated nickel or cobalt acetates in methanol to form alpha-pyridilic acid metal complexes which are highly stable and require severe acid treatment for decarboxylation.[6]

No reports of reactions analogous to the benzilic acid rearrangement using pyridyl-substituted diketones under acidic conditions exist in the literature.

DISCUSSION

General

Alpha-pyridil, when treated with aqueous hydrochloric acid and heated under reflux at 90° for two hours, gave a product, $C_{12}H_{12}N_2O_3Cl_2$; this result indicated addition of one molecule of water and two of hydrogen chloride to the starting compound.[2] The product was explained by a rearrangement of the benzilic acid type by alpha-pyridil. The postulated rearrangement mechanism is shown in equation (3). It was assumed that alpha-pyridil took up two



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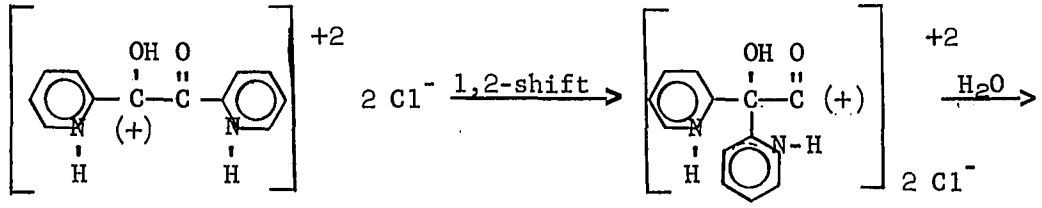

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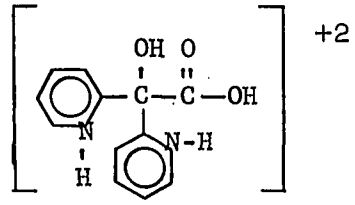


(3)

V

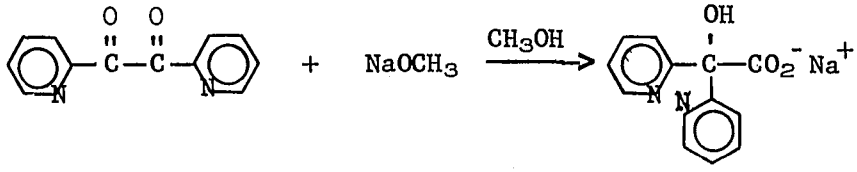
molecules of hydrogen chloride to yield alpha-pyridil dihydrochloride, and refluxing the solution promotes formation of a carbonium ion, (III). A 1,2-shift of a pyridyl group from the second carbonyl group to the first one which was positively charged could then occur, thus producing another carbonium ion, with the positive charge on the carbonyl, (IV). This compound could have easily taken up a hydroxyl ion from water to yield the rearranged product, (V), which was called "alpha-pyridilic acid dihydrochloride." The identification of the product was based on elemental analysis and the dissimilarities between its infrared spectrum and that of alpha-pyridil.[2]

Preparation of Derivatives

In order to characterize the product of Barakeh's work, attempts to prepare carboxylic acid derivatives of "alpha-pyridilic acid dihydrochloride" were made. Two different methods were used to prepare the benzoate ester of compound (V), both of which yielded only benzoic acid. The compound was reacted with phenacyl bromide with the intention of preparing the phenacyl ester; this reaction gave no ester product. An attempt to prepare the ethyl ester and the anilide were also unsatisfactory. Hence it was observed that "alpha-pyridilic acid dihydrochloride" did not form well-known carboxylic acid derivatives, perhaps because of decomposition, as the solutions invariably darkened to a deep brown color during the reactions.

Other Reactions

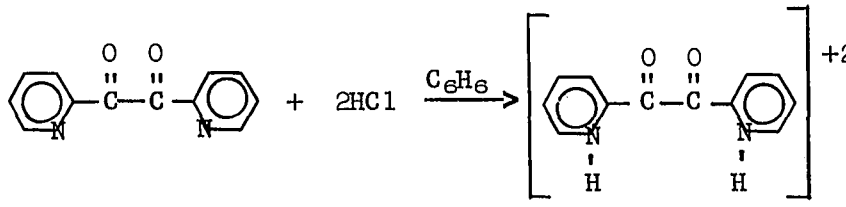
An independent synthesis of "alpha-pyridilic acid dihydrochloride" was attempted by making use of the sodium salt as prepared by Klosa.[4]



(4)

The salt was found to be unstable when isolated; addition of hydrogen chloride to a methanol solution of the sodium salt resulted in a deep brown solution which gave no solid products upon evaporation.

A benzene solution of alpha-pyridil was treated with hydrogen chloride in order to obtain alpha-pyridil dihydrochloride needed for comparison purposes, according to equation (5). The reaction went



(5)

in good yield to give a product which appeared to be surprisingly similar to that produced by Barakeh.[2] However, rearrangement with addition of a molecule of water was impossible since water was excluded from the reaction. A careful examination of the infrared spectra, elemental analysis, and physical properties of the two compounds showed them to be almost identical; they were identified as alpha-pyridil dihydrochloride and alpha-pyridil dihydrochloride monohydrate, respectively.

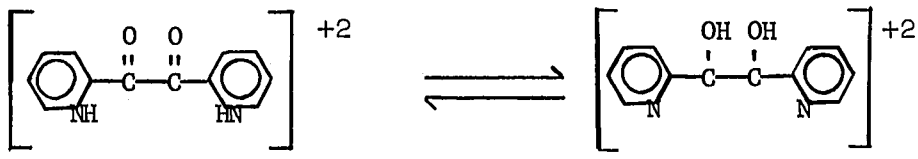
Alpha-pyridil reacts with strong base in a benzilic acid type rearrangement with subsequent decomposition to form dipyridyl carbinol (See equation 2).[2,5] Barakeh also reported decomposition of "alpha-pyridilic acid dihydrochloride" to give dipyridyl carbinol.[2] It was observed in the present investigation that careful addition of

sodium carbonate to an aqueous solution of "alpha-pyridilic acid dihydrochloride" resulted in formation of alpha-pyridil, with evolution of a gas thought to be carbon dioxide. Thus the reversibility of Barakeh's postulated rearrangement is shown; this very fact detracts strongly from the suggestion that an acid-catalyzed benzilic acid type rearrangement had taken place, as one would not expect such a rearrangement to be reversible. Probably the formation of dipyridyl carbinol that Barakeh observed resulted from the reaction of alpha-pyridil, formed by addition of base to the dihydrochloride, with strong base to yield alpha-dipyridyl carbinol.

Alpha-pyridil was refluxed with aqueous hydriodic acid under the same conditions as the similar hydrochloric acid reaction, and a yellow solid was isolated in low yields. The solid was identified as alpha-pyridil dihydroiodide monohydrate on the basis of its elemental analysis and the similarity of its infrared spectrum and physical properties to those of alpha-pyridil dihydrochloride monohydrate.

Infrared Spectrum

The principal infrared absorbances of alpha-pyridil and alpha-pyridil dihydrochloride monohydrate are shown in Table I. It is observed that the carbonyl stretching frequency is conspicuously missing from the spectrum of alpha-pyridil dihydrochloride monohydrate. This fact indicates addition of the protons to the carbonyl oxygens, or at least some kind of equilibrium between the forms shown below.



Probably the actual structure lies somewhere between the two shown.

Work on the molecular configuration of alpha-pyridil has shown that the molecule consists of two planes each of which includes a pyridine ring, a carbonyl group, and its adjacent carbon atom, the angle between the two planes being 83°.[7] The fact that the two carbonyl groups are not coplanar leads to the conclusion that there should be two carbonyl stretching frequencies observed in the infrared, as was indeed observed by Bernal in 1961.[8] Since both these frequencies are missing in the spectrum of the hydrochloride salt, it can be concluded that both carbonyl oxygens are protonated in the solid state, perhaps accounting for the broad peak in the hydroxyl stretching range. The fact that the spectra of the dihydrochloride and the hydrated dihydrochloride are identical except in the hydroxyl region lends further support to this argument.

Table I. Principal Infrared Absorbances[9] (cm^{-1})

	Alpha-pyridil	Alpha-pyridil dihydrochloride monohydrate
	3380 (med)	3020 to 3220 (broad)
	3070 (sharp)	
1725 to	1690 (doublet)	1625 (sharp)
	1590 (sharp)	1515 (sharp)
	1470 (sharp)	
	1440 (sharp)	
	1340 (sharp)	
1300 to	1270 (triplet)	
	1220 (med)	1200 (sharp)
		1143 (med)
	1088 (sharp)	1082 (med)
	1040 (sharp)	1035 (med)
	995 (sharp)	
	915 (sharp)	
	895 (med)	
	788 (sharp)	755 (med)
740 to	755 (doublet)	
	705 (broad)	

(KBr discs)

EXPERIMENTAL PART

Preparation of "Alpha-Pyridilic Acid Dihydrochloride"

The method of Barakeh was used for preparing this compound.[2] In a 500 ml. 3-neck round-bottomed flask fitted with a stirrer, reflux condenser, and thermometer were mixed 23 g. of alpha-pyridil, 113 ml. of concentrated hydrochloric acid, and 113 ml. of distilled water. The mixture was heated, with stirring, to 104°, at which time all of the alpha-pyridil had dissolved; and then the temperature was lowered to 90°, where it was maintained for 2 1/2 hours. The crystals of alpha-pyridil dissolved gradually as the temperature was raised, and as the temperature approached 104°, all of the alpha-pyridil dissolved. The color of the solution changed gradually from yellow to dark red-brown, resembling concentrated permanganate solution. After 2 1/2 hours, the apparatus was disassembled, and the reaction mixture was poured into a 400 ml. beaker, covered with a watch glass, and allowed to cool. No crystals formed at this stage, but after the solution stood for two days, a small amount of crystalline solid was observed. The aqueous solution was evaporated to a small volume on a steam cone with the aid of a stream of air, and then filtered. The brown crystals were recrystallized twice by dissolving them in a minimum amount of distilled water, adding approximately 1 1/2 volumes of concentrated hydrochloric acid, stirring the mixture with a glass rod, and cooling it in an ice bath; the crystals thus obtained were separated by vacuum filtration and dried in a vacuum desiccator at room temperature overnight. The combined

filtrates were evaporated to a small volume on a steam cone with the aid of a stream of air. The resulting solid was separated by vacuum filtration, dissolved in a minimum amount of water, and 1 1/2 volumes of concentrated hydrochloric acid was added; the mixture was cooled in an ice bath with stirring, and the product was collected as before. This operation was repeated twice, and the crystals thus obtained were dried as before and added to those obtained above.

When crystallized in this manner, the compound is pink-brown in color; it has a pleasant odor but irritates the nose and causes one to sneeze.

The yield was 48% with a melting point of 179-182° in a sealed tube. This melting point is only approximate since the material decomposes and the color darkens before melting, even in a sealed tube. However, these observations agree with those of Barakeh.[2]

The infrared spectrum was found to be identical to that obtained by Barakeh. The elemental analysis is given below.[10]

Calc. for $C_{12}H_{14}N_2O_4Cl_2$	C 44.87	H 4.39
Found for "	C 44.92	H 4.62
Barakeh[2] for "	C 44.86	H 4.36

Attempted Preparation of Esters

To a 1 g. sample of the compound thought to be a carboxylic acid, dissolved in 3 ml. of anhydrous pyridine, was added .5 g. of benzoyl chloride. The pyridine was heated to dissolve the compound. When benzoyl chloride was added, a white solid formed, and

the color of the solution changed from orange to green. The mixture was heated on a steam cone for one minute, and the white solid dissolved. The hot solution was poured into 10 ml. of water, with vigorous stirring. The aqueous solution was cooled and filtered; a white solid was collected by vacuum filtration and was recrystallized from hot 95% ethanol. It was identified as benzoic acid from its melting point (119-121) and infrared spectrum.

One gram of compound was mixed with .5 ml. benzoyl chloride and heated to boiling over a low flame. A dark green solution resulted, which turned dark orange upon standing. The solution was poured into 10 ml. of water, and a dark brown oil appeared. After the mixture stood for two days, crystals appeared, and were separated by vacuum filtration. The white solid was recrystallized from hot 95% ethanol and was identified as benzoic acid.

One gram of the compound was dissolved in 5 ml. of water; 10 ml. of absolute ethanol and 1 g. of phenacyl bromide were added, and the mixture was refluxed for 80 minutes. The mixture was then poured into 50 ml. of cold water, but no solid appeared, even after cooling. The solution was evaporated on a steam cone, and a dark brown, viscous material resulted. No solid product could be obtained.

One gram of the compound was dissolved in 5 ml. of aniline and heated to 100°. The solution was filtered and evaporated on a steam cone to a small volume; only a dark brown oil resulted.

One gram of the compound was dissolved in 20 ml. of absolute ethanol, 1 drop of concentrated sulfuric acid was added, and the solution was evaporated to a small volume on a steam cone and gave a brown oil which could not be purified.

Other Reactions

Preparation of Sodium Salt of Alpha-Pyridilic Acid. The method of Klosa[4] was followed to prepare the sodium salt of alpha-pyridilic acid. Alpha-pyridil (10.6 g.) was dissolved in 946 ml. of methanol; 0.7 g. of sodium metal was dissolved in 200 ml. of the solution, and the resulting solution was heated for 4 hours, and then allowed to cool. Since no crystals appeared, solvent was distilled from the solution. After 55 ml. of methanol had been collected, white crystals formed in the distilling flask. The crude material was collected by vacuum filtration; it melted over a broad range and decomposed to a brown oil upon standing.

Attempted Preparation of "Alpha-Pyridilic Acid Dihydrochloride" from the Sodium Salt. The sodium salt of alpha-pyridilic acid was prepared as described above and left in the methanol; dry hydrogen chloride was bubbled through the solution for a period of 1/2 hour. The solution was a faint yellow color initially, but it instantly turned red-orange when hydrogen chloride first contacted it. The color quickly reverted to faint yellow and then gradually disappeared. No solid product could be isolated after the solution was evaporated to a small volume on a steam cone. Sodium-dried benzene (250 ml.) was added to the residue, resulting in the appearance of a finely divided white solid, which was separated by vacuum filtration. This solid was thought to be sodium methoxide on the basis of its solubility in water and its broad decomposition range (145-160°). No other solid product was isolated.

Reaction of Alpha-Pyridil and Hydrogen Chloride in Benzene. Sodium-dried benzene (150 ml.) was saturated with alpha-pyridil, and anhydrous hydrogen chloride was bubbled through the solution. Crystals formed instantly and hydrogen chloride addition was continued until no new crystal formation was observed. The product was yellow-orange in color; it was collected by vacuum filtration, washed with benzene, and dried in a vacuum desiccator. Addition of silver nitrate solution to an aqueous solution of the product gave a white precipitate, indicating the presence of chloride ion. The product was identified as alpha-pyridil dihydrochloride on the basis of the presence of chloride ion, its melting point (180-182°, with decomposition; lit.[10] 182-183°, with decomposition), and the following elemental analysis.[11]

Calc. for $C_{12}H_{10}N_2O_2Cl_2$	C 50.53	H 3.51	N 9.83
Found for "	C 51.26	H 3.36	N 10.37

The infrared spectrum of alpha-pyridil dihydrochloride was almost identical to that of "alpha-pyridilic acid dihydrochloride" as reported by Barakeh[2]; the only difference was a sharper band in the hydroxyl region for alpha-pyridil dihydrochloride.

Reaction of "Alpha-Pyridilic Acid Dihydrochloride" with Sodium Carbonate. To 25 ml. of water was added 3 g. of "alpha-pyridilic acid dihydrochloride;" sodium carbonate was added to the solution until it was basic to litmus. A cream-colored solid formed in the yellow solution and was collected by vacuum filtration, and was allowed to dry. The product was identified as alpha-pyridil by its melting point (154.5°) and its infrared spectrum. The yield was 1.9 g. (76%).

This reaction was repeated with alpha-pyridil dihydrochloride, and identical results were obtained.

Reaction of Alpha-Pyridil with Hydriodic Acid. In a 500 ml. round-bottomed flask fitted with a stirrer, reflux condenser, and thermometer were mixed 21 g. of alpha-pyridil, 50 ml. of 57% hydriodic acid, and 50 ml. of water. A brown solution resulted immediately, and the temperature rose to 50°. The solution was stirred for one hour without application of heat, and then was heated, with stirring, to 90°; this temperature was maintained for 3 hours, with stirring during that time. The solution was then poured into a 250 ml. beaker, covered with a watch glass, and allowed to cool. Yellow-brown crystals appeared upon standing and were collected by vacuum filtration. The material was recrystallized from hot 95% ethanol to give a yellow solid, melting point 180° with decomposition. Addition of silver nitrate solution to an aqueous solution of the product gave a cream-colored precipitate, indicating the presence of iodide ion. The solid was identified as alpha-pyridil dihydroiodide monohydrate on the basis of the presence of iodide ion, the close similarity of its infrared spectrum to that of alpha-pyridil dihydrochloride monohydrate, and the following elemental analysis.[11] The yield was 4.73 g. (9.85%).

Calc. for $C_{12}H_{12}N_2O_3I_2$	C 29.60	H 2.47	N 5.75
Found for "	C 30.58	H 2.45	N 6.11

SUMMARY

This investigation was concerned with the chemical nature of the product of a recently-reported novel rearrangement called the alpha-pyridilic acid rearrangement. The product of this rearrangement was thought to be the dihydrochloride of a previously unknown compound, alpha-pyridilic acid. Attempts by this investigator to prepare carboxylic acid derivatives of "alpha-pyridilic acid dihydrochloride" were completely unsuccessful. The compound was shown to be in fact alpha-pyridil dihydrochloride monohydrate by regeneration of the starting alpha-pyridil with addition of sodium carbonate to an aqueous solution of the former compound. It is interesting to note that the empirical formulas of alpha-pyridilic acid dihydrochloride and alpha-pyridil dihydrochloride monohydrate are identical; hence, one could be easily mistaken for the other, since very little is known about either one. Alpha-pyridil dihydrochloride, anhydrous, was prepared for the sake of comparison, as was a previously unreported compound, alpha-pyridil dihydroiodide monohydrate. Infrared spectra of these three compounds showed them all to be very similar in structure; however, their spectra are vastly different from that of the parent compound, alpha-pyridil. A possible explanation was offered for this dissimilarity in infrared spectra, based on the determination of molecular structure of alpha-pyridil.[7] It has been calculated that alpha-pyridil is a skewed molecule, with an angle of 83° between the planes of each ring.

This configuration gives rise to two carbonyl bands in the infrared,[8] both of which are absent in the hydrochloride and hydroiodide salts of alpha-pyridil: Perhaps this absence is due to protonation of both carbonyl oxygens when the compound is in its solid state.

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II. THE CHEMISTRY OF MIXED ALIPHATIC-AROMATIC TERTIARY AMIDES

INTRODUCTION

Surprisingly little mention is encountered in the modern literature of the acylation of amides to form the compounds known as tertiary amides; other methods of preparation are few, and even less research has been done concerning chemical properties of these compounds. Probably a major deterrent to work in this area is the difficulty with which the compounds are prepared. The first mention of tertiary amides was that of triacetamide, in 1870,[1] although the compound probably was not actually prepared until 1890,[2] when tribenzamide was also first prepared.[3] Other members of the tertiary amide class, such as N-acylphthalimides, are more widely known, and are commonly recommended as derivatives for the characterization of acyl halides.[4] To date, Thompson has devised the most satisfactory general method for synthesis of tertiary amides, particularly those with mixed acyl groups, by employing what he calls "direct diacylation" of primary amides.[5]

Direct diacylation has been mentioned only in a few other isolated cases,[6,7,8] and in all of these, the use of pyridine, or a comparable base, was shown to be a necessity. It is thought that an acyl halide-pyridine complex is responsible for the direct diacylation.[5]

It has been observed in this laboratory that tertiary amides have a characteristic absorbance in the region of 5.85 microns,[9,10] the location of the aldehydic and ketonic carbonyl. In order to elucidate the chemistry of tertiary amides, it is necessary to

determine whether they react as true carbonyl compounds, in contrast to the behavior of primary amides and other carboxylic chalcogen derivatives.

Interpretation of spectral data and chemical and physical properties poses interesting problems concerning the structure of these compounds. The goal of the present investigation was the determination of the chemical behavior and structure of tertiary amides and related compounds. The carbonyl system, whether ketonic or amide-like, undergoes nucleophilic attack by such reagents as amines, alcohols, hydrazines, bases, Grignard reagents, as well as reduction reactions. A number of these reactions were investigated for a typical mixed aliphatic-aromatic tertiary amide, and the results are reported herein.

HISTORICAL PART

General

A careful search of the literature from 1809 to the present yielded only two references to N-acetyldibenzamide, and only a few to other tertiary amides. Most of these references dealt only with the synthesis of these compounds and not with their chemistry.

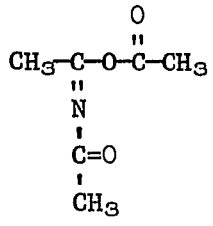
It must be mentioned that there may exist some confusion regarding nomenclature of tertiary amides. The designation "tertiary amide" is well established and approved by the IUPAC for the N,N-diacylamides,[5,11] but the term has occasionally been used to designate N,N-dialkylamides.[12] The name "triacylamine" seems inappropriate because of the probable dissimilarity between these compounds and true amines. Throughout this dissertation, the term "tertiary amide" is used to designate N,N-diacylamides.

The simplest known member of the tertiary amide series is triacetamide, first reported in 1870 by Wichelhaus, who heated acetic anhydride with acetonitrile and obtained a product melting at 78-79°;[1] although his yields were low, the reaction has been cited several times[11,13,14] as a general method of synthesis of tertiary amides. The reaction has never been successfully employed in this laboratory.

A subsequent investigator studied the reaction of the sodium salt of diacetamide with acetyl chloride and also obtained a low yield of a substance melting at 77°.[15] More recently, triacetamide was prepared by Kocheshkov by reaction of ketene with diacetamide;

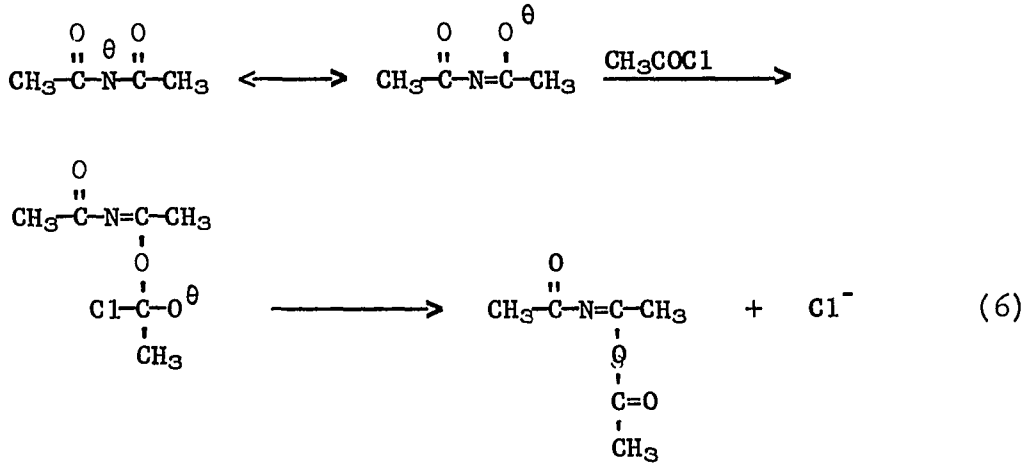
a melting point of 8° was reported, with the comment that repeated attempts to duplicate Wichelhaus' work led instead to diacetamide with a melting point of 78°.[16] Work in this laboratory has substantiated Kocheshkov's observation of the melting point of triacetamide.[9] Bell obtained his product by the reaction of diacetamide and isopropenyl acetate, and found the melting point to be 8°. He was unable to duplicate Wichelhaus' work.

It seems plausible that triacetamide was probably first prepared by Hentschel from acetic anhydride and diacetamide,[2] and the same compound was subsequently obtained by Brunner from potassium cyanate and acetic anhydride.[17] In view of the work of Wichelhaus, Brunner proposed that his compound, which melted at 8°, had the following structure:[17]



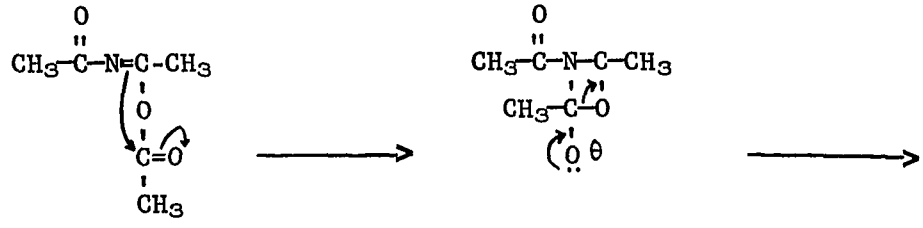
However, the work of Kocheshkov[16], and observations in this laboratory support the triacylamine structure.

It is highly probable that Wichelhaus[1] and Rakshit[15] actually prepared the isomeric imidoester shown above. Wichelhaus' method could understandably have given the indicated structure, as could Rakshit's, if O-acylation if favored over N-acylation in the sodium derivative of diacetamide, according to the following scheme.



(6)

It is suggested by Kocheshkov that the imidoester structure is an intermediate in his preparation of triacetamide;[16] thus he believes that ketene reacts with the lactim (imide) form of diacetamide, but that the resulting O-acyl structure immediately tautomerizes to the tertiary amide.



$(CH_3CO)_3N$ (7)

Except for five mixed aliphatic tertiary amides prepared by Kocheshkov,[16] and trimethacrylamide prepared by Lalonde and Aksentijevich,[18] no other purely aliphatic representatives of this class have been reported prior to this dissertation.

Aromatic tertiary amides are somewhat better known, tribenzamide being mentioned more often than other tertiary amides in the literature.

Tribenzamide was first prepared by Curtius in 1890 by the reaction of benzoyl chloride with benzamide.[3] Tribenzamide was reported to be a side product in 1893 by Jaffe in the preparation of benzamide by the action of ammonium carbonate on benzoyl chloride.[19] The compound was also prepared by Wheeler, in 1898, by the reaction of acetobenzimidoethylic ether and benzoyl chloride at temperatures of 100-120°.[20] In the same year, Blacher reported a preparation of tribenzamide by reaction of benzoyl chloride with a suspension of sodium benzamide in xylol.[21] Brunner obtained small yields of tribenzamide, benzonitrile, and dibenzamide by the reaction of benzoic anhydride with potassium cyanate.[17]

In 1910, Garrod and Hurtley treated urine with benzoyl chloride and thought they had isolated a benzoyl-tryptophan derivative[22], but Ellinger and Riesser showed that the product of this reaction was tribenzamide.[23]

The next mention of tribenzamide occurred in 1938, when Parts reported the heat of combustion of tribenzamide to be 2425.5 Kcal/mole.[24]

Yasamura, in 1951, reported the preparation of tribenzamide by the hydrolysis of benzyl (sic) chloride with ammonium hydroxide.[25] Thompson obtained tribenzamide, as well as a number of other tertiary amides, by the direct diacylation of benzamide with benzoyl chloride after complexing the acyl halide with pyridine.[5]

A reaction of lithium nitride and benzoyl chloride in diethylene glycol dimethyl ether produced tribenzamide as one product in 1961.[26] Farrar, in 1960, prepared tribenzamide by reacting 2,4,5-trichlorobenzenesulfonyl chloride and dibenzamide in pyridine

at 100° for 24 hours.[27] Recently, the synthesis of tris(m-triflouromethyl)tribenzamide was reported in the literature.[28]

Even less mention is made in the literature of a third class of tertiary amides--the mixed aliphatic-aromatic tertiary amides. This class is characterized by a combination of aliphatic and aromatic acyl groups surrounding the central nitrogen atom. The first known members of this class were not reported until 1951, when Thompson prepared eleven diaroyl acetamides.[5] Since then, there has been but one other mention of this class of tertiary amides, that being by Tyka who performed a Friedel-Crafts reaction with N-acetyldibenzamide and obtained acetophenone.[29]

It is interesting that the best reported method[5] of preparing tertiary amides is said to involve direct diacylation, and that this phenomenon seems to occur only in the presence of pyridine and other tertiary amines comparable to pyridine in basicity. The first mention of a similar reaction occurred in 1892, when Minnuni prepared benzoic anhydride in 78% yield by the reaction of a mixture of benzoyl chloride and pyridine with water.[6] Much later, in 1949, Adkins and Thompson reported the preparation of pyridine complexes of furoyl chloride, acetyl chloride, benzoyl chloride, propionyl chloride, and the triethylamine complexes of propionyl chloride, acetyl chloride, and furoyl chloride.[8] These complexes reacted with water and hydrogen sulfide at low temperatures to form the respective anhydrides and thioanhydrides in good yields.[8] Thompson has suggested that these same addition complexes are responsible for the direct diacylation of primary amides at low temperatures to form tertiary amides.[5] W. von E. Doering and W.E. McEwen have postulated such complexes as

intermediates in the alkylation of pyridine.[30] In 1953, Baumgarten reported the preparation of cinnamoylpyridium chloride, which reacted with water or dilute base to give the anhydride.[31] F. Klages and E. Zange reported the observation of the powerful acylating properties of $(RCONR_3)^+SbCl_6^-$, a similar complex, in 1957.[32]

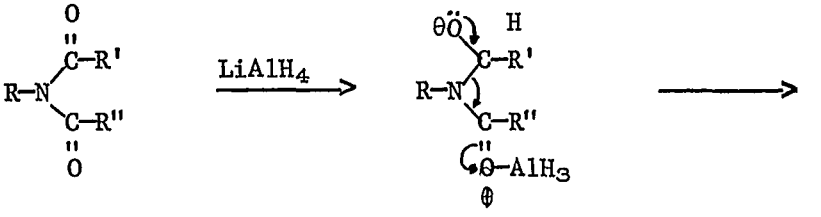
Reactions of Tertiary Amides

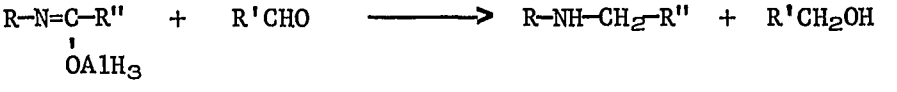
The infrequent mention of tertiary amides has given rise to only fragmentary data in the literature on the chemical behavior of these compounds. Curtius reported that tribenzamide sublimes without decomposition, and that it is cleaved by sodium hydroxide to give ammonia and sodium benzoate.[3] Brunner noted the facile hydrolysis of triacetamide.[17] Kocheshkov reported that triacetamide "easily acetylates water, alcohols, amines, acetic acid, and acetamide," that all three acyl groups are equivalent in the sense that any one of the three will participate in acylation reactions (supporting the triacylamine structure), and that the aliphatic tertiary amides generally react as do acid anhydrides, e.g., will undergo trans-acylation and will produce ketenes on being heated.[16] As mentioned above, Tyka has employed N-acetyldibenzamide, as well as tribenzamide, in Friedel-Crafts acylation of benzene.[29] No other reference to the chemical behavior of tertiary amides is made in the literature.

Reduction Reactions

Although no mention of direct reduction of tertiary amides can be found in the literature, several reduction reactions are cited which might be expected to be analogous to tertiary amide reduction.

In 1952, Witkop and Patrick reported the lithium hydride reduction of secondary amides to produce N-alkylamides.[33] The lithium aluminum





(8)

hydride reduction of N-alkyl-and N-phenyl-succinimides to N-substituted pyrrolidines, and in some cases, to both the substituted pyrrolidines and to amino alcohols, was reported by Schreiber and Fernandez in 1961.[34] These a hors also reduced succinamic acids by the same method.[34] As mentioned earlier, work in this laboratory on the reduction of tertiary amides is the first such work reported.[9,10,35] Reduction of tribenzamide with lithium aluminum hydride produced N-benzylbenzamide,[36] and the analogous reaction with 4,4'4"-trichlorotribenzamide gave p-chlorobenzyl-p-chlorobenzamide.[35] These reductions were thus analogous to that reported for secondary amides.[33]

In 1958, Brown and Rao synthesized aldehydes by reduction of acid chlorides by lithium tri-t-butoxyaluminohydride.[37] They state that the introduction of alkoxy substitutients into lithium aluminum hydride moderates the reducing capacity of this reagent.[37] Aldehydes were obtained in high yields by the following reaction.

$$R\text{—}CO\text{—}Cl + LiAlH[OC(CH_3)_3]_3 \longrightarrow R\text{—}CHO + Al[OC(CH_3)_3]_3 + HCl \quad (9)$$

It is possible that the carbonyl group of the tertiary amide might undergo a reduction similar to that described above, since the diamide anion has been found to act much like the chloride ion in the facility with which it is cleaved from the molecule.

In 1959, a similar reduction was applied to N,N-dimethylamides by Brown and Tsukamoto.[12] They obtained high yields of aldehydes by the use of lithium diethoxyaluminohydride as a selective reducing agent.

In the same year, Zakharkin and Khorlina synthesized aldehydes by the reduction of dialkylamides with diisobutylaluminum hydride.[38] In 1962, these same authors reported the reduction of esters to aldehydes, using the same hydride as the reducing agent.[39]

Tyka reduced the phosphorus analog of tribenzamide using lithium aluminum hydride, and obtained benzyl alcohol and a small amount of $(C_6H_5CHOH)_3P$.[29]

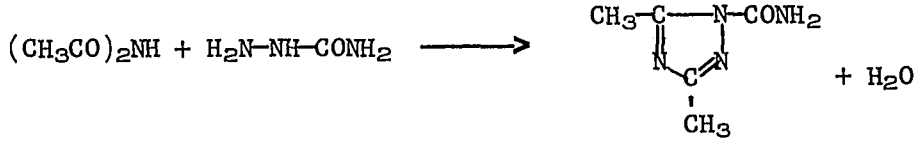
Diborane has been a popular reducing agent in recent years. In 1960, Brown and Rao employed diborane in the reduction of a number of representative organic compounds, including carboxylic acids, aldehydes, esters, and ketones, to alcohols, and in the reduction of nitriles to amines.[40] N-Alkyl- and N,N-dialkylamides were reduced rapidly under relatively mild conditions by the use of diborane.[41] In all cases, the amides were reduced to the corresponding alcohols in high yields. Cowart employed diborane in the reduction of 4,4',4''-trichlorotribenzamide in 1965.[35] One of the

products he obtained was N-(p-chlorobenzyl)-p-chlorobenzamide, the same product as that obtained from the lithium aluminum hydride reduction.[35] Another product obtained was not identified. Ieyoub reduced tribenzamide with sodium borohydride and produced N-benzylbenzamide.[36]

In 1961, Dale reduced acyclic 1,3-diketones to the corresponding 1,3-diols in excellent yields by the use of sodium borohydride.[43] Chaiken and Brown found sodium borohydride in water or methyl alcohol to be effective in the reduction of aldehydes and ketones to the corresponding alcohols.[42] They also found that sodium borohydride in dioxane or diethyl carbitol would reduce acid chlorides, but that carboxylic acids and acid anhydrides show only slight reduction on prolonged heating; esters and nitriles were hardly effected.[42]

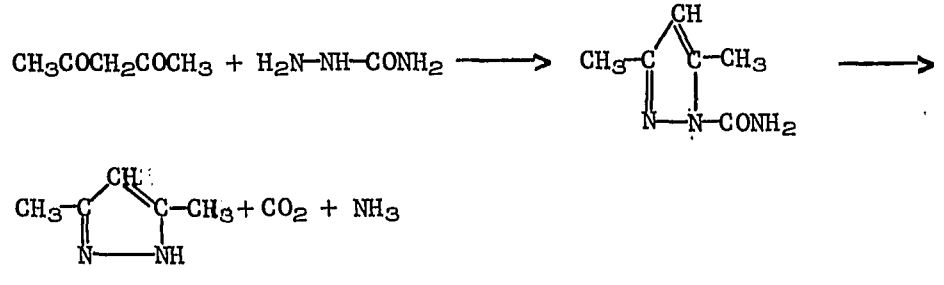
Hydrazine Reactions

In 1951, Brunner reacted secondary amides with hydrazine and obtained substituted triazoles.[45] Similarly, he reacted diacetamide with semicarbazide and obtained a cyclic compound:[45]



(10)

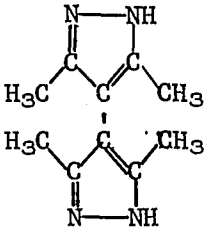
He reacted acetylacetone and semicarbazide as follows:[45]



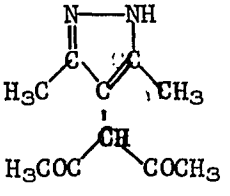
(11)

In the following year, Wolchowe reported that the reaction of dibenzamide and phenylhydrazine hydrochloride yielded 1,3,5-triphenyl-1,2,4-triazol.[46]

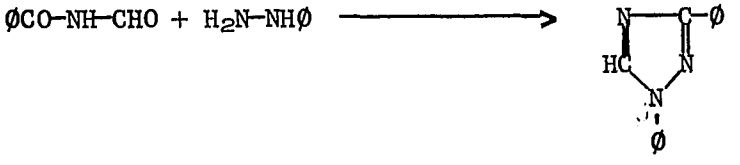
In 1957, Mosby reported the reaction between 3,4-diacetylhexane-2,5-dione and excess hydrazine yielded a cyclic compound:[47]



A single equivalent of hydrazine gave the following product:[47]



Thompson has reported the reaction of N-formylbenzamide and phenylhydrazine to proceed as follows:[5]



(12)

Work in this laboratory has shown that tertiary amides react with hydrazine in quite a different manner.[9,10,35] Rather than forming the expected triazoles, they gave symmetrical diacylhydrazines. From

the discussion on page 36 of this dissertation, it might have been anticipated that tertiary amides would be excellent acylating agents because of steric hindrance about the nitrogen atom. N-Acetyldibenzamide was reacted with a variety of amines as part of this investigation in order to test the acylating ability of tertiary amides.

Grignard Reactions

The first reported Grignard reactions performed with tertiary amides were in this laboratory. It has been shown that aromatic Grignard reagents react with tertiary amides to yield tertiary alcohols, while aliphatic Grignard reagents produce ketones.[9,10,35]

Alcoholysis and Ammonolysis

Only recently has alcoholysis of tertiary amides been performed.[35,36] By reacting ethanol with 4,4',4"-trichlorotribenzamide, Cowart obtained the expected ester and p-chlorobenzamide, contaminated with secondary amide.[35] Ieyoub had similar results with the ethanolysis of tribenzamide,[36] as did Tyka with the ethanolysis of tribenzoylphosphine.[29]

It is commonly known that esters can be prepared by the reaction of anhydrides with alcohol. Reid, in 1909, performed the alcoholysis of benzamide and the nitrobenzamides, using hydrochloric acid as a catalyst. He found that the amides were converted to the corresponding esters.[48]

Acid anhydrides, when treated with ammonia, are converted to primary amides and ammonium salts.[49] The only reported ammonolysis

of tertiary amides was carried out recently.[9,35,36] The expected products, primary amide and secondary amide, were obtained.

$$(RCO)_3N + NH_3 \longrightarrow R\text{-}CONH_2 + (RCO)_2NH \qquad (13)$$

Ammonolysis of tribenzolyphosphine also yielded benzamide.[29]

Bromination and Reaction with Sulfuric Acid

Tyka performed reactions with tribenzoylphosphine which furnished results closely associated with the results expected from the similar reactions of tertiary amides. In 1963 he reacted tribenzoylphosphine with three molar equivalents of bromine and obtained three molar equivalents of benzoyl bromide and one molar equivalent of phosphorus tribromide.[29]

Tyka also described the reaction between tribenzoylphosphine and sulfuric acid:

$$(\phi CO)_3P + H_2SO_4 \longrightarrow PH_3 + 3\ \phi CO_2SO_3H \longrightarrow 3\ \phi CO_2H + 3\ H_2SO_4 \qquad (14)$$

These transformations were performed as part of this investigation using N-acetyldibenzamide instead of tribenzoylphosphine as the substrate.

Pyrolysis

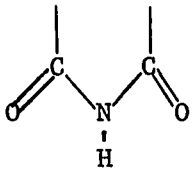
Curtius reported that tribenzamide sublimed undecomposed.[3] Results from this laboratory show contradiction, as Ieyoub has shown

that heating of tribenzamide leads to pyrolysis, rather than sublimation, to give benzonitrile.[36]

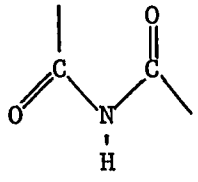
DISCUSSION

General

One of the most interesting aspects of the study of tertiary amides is the difficulty with which these compounds are prepared. In the case of secondary amides, the placement of the two acyl groups around the central nitrogen atom is relatively easy; in the case of diacetamide, two planar structures exist. Indeed, these two isomers have been isolated and their infrared spectra studied.[50] The two planar structures are shown below.



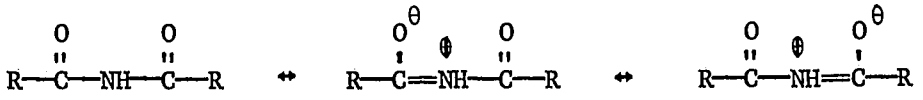
trans-trans



cis-trans

If tertiary amides are likewise planar, a difficult problem arises in the placement of three acyl groups around nitrogen in such a sterically disfavored arrangement. This difficulty forces one to consider the possibility of a pyramidal structure for tertiary amides.

Resonance factors must also be considered in a discussion of stability of tertiary amides. The stability of primary and secondary amides is enhanced by resonance contributions such as the following.



Such resonance would be inhibited by addition of a third acyl group, as in the case of tertiary amides, since co-planarity becomes sterically disfavored.

In the best method reported for the synthesis of tertiary amides, Thompson produced various tertiary, including N-acetyldibenzamide, by reacting the acid chloride and the primary amide in pyridine, using chloroform as the solvent, at low temperatures.[5] He suggests that the tertiary amides are produced as a result of direct diacylation of the primary amide by acid chloride, since dibenzamide and benzoyl chloride did not react under the same experimental conditions to yield tertiary amide.[5]

Acylpyridinium Chloride Complexes

It is interesting to note that in all the cases of direct diacylation reported in the literature, pyridine, or a tertiary amine of comparable basicity, was present in the reaction mixture. When Minnuni[6] prepared benzoic anhydride by reaction of a mixture of benzoyl chloride and pyridine with water, he formulated the reaction as shown below.

$$2\ \text{Ø—CO—Cl}\cdot C_5H_5N + H_2O \longrightarrow (\text{Ø—CO})_2O + 2\ C_5H_5N\cdot HCl \qquad (15)$$

The equation suggests the formation of a benzoyl chloride-pyridine complex. Wedekind[7] suggested that a radical was formed from the acyl chloride by the removal of the elements of hydrogen chloride to give C_5H_5NHCl. His postulated radical, $R\text{—}\dot{C}\text{—}\dot{C}{=}O$, would be equivalent to a ketene. The fact that Staudinger prepared diphenyl ketene in quantitative yield through the reaction of diphenylacetyl chloride and tripropylamine[51] lends credence to Wedekind's suggestion,[7] at least for acyl chlorides containing alpha-hydrogens. In fact, Hanford and Sauer have summarized work on the preparation of a variety of

ketenes by this method.[52] In his earlier work, Thompson prepared the pyridine complexes of furoyl chloride, acetyl chloride, benzoyl chloride, and propionyl chloride, and the triethylamine complexes of propionyl chloride, acetyl chloride, and furoyl chloride.[8] All of these were prepared in petroleum ether at temperatures of -20°. Reaction of these complexes with water and hydrogen sulfide produced acid anhydrides and thioanhydrides, respectively.[8] Thompson found that the preparations of the complexes proceed in highest yields if the reaction mixture is free of water or organic acid;[8] his best yields in reactions of the complexes were obtained by first forming the addition compound in petroleum ether at low temperatures, and then hydrolyzing it with 1/2 mole of water per mole of acyl chloride.[8]

Formation of anhydride cannot be formulated as depending upon the intermediate formation of ketene in the case of benzoyl and other aroyl chlorides, as it is impossible for them to undergo dehydrohalogenation and subsequent generation of ketene. Moreover, Thompson found that triethylamine, the preferred reagent for dehydrohalogenating acyl halides to ketenes, is inferior to pyridine for the preparation of anhydrides.[8] Further work in this area was performed by Baumgarten, who prepared cinnamoylpyridinium chloride by reacting cinnamoyl chloride with a slight excess of pyridine in anhydrous diethyl ether at low temperatures. This complex reacted with water or dilute base to give the acid anhydride.[31]

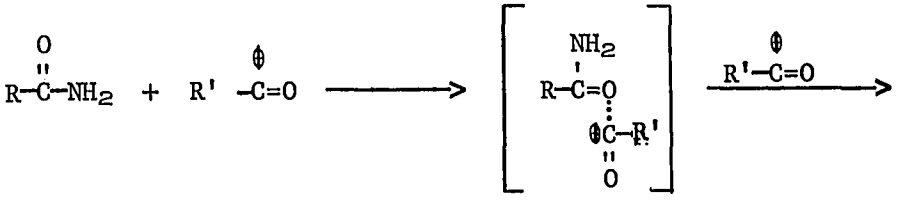
In correlation with the above information, it is interesting to note that there has been no report of direct diacylation of primary amides by acyl chlorides capable of forming ketenes easily. Thus,

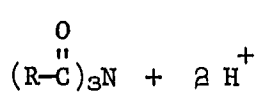
only benzoyl chloride, variously substituted benzoyl chlorides, and cinnamoyl chloride have been observed to diacylate primary amides;[5] however, acetyl chloride- and propionyl chloride-pyridine complexes, as well as those of aroyl chlorides, have been reported to diacylate water and hydrogen sulfide.[8]

This author believes that the phenomenon of diacylation might be explained by considering the reactivity of the acyl halide-pyridine complex and the relative nucleophilicity of the nitrogen atom in primary and secondary amides as compared to oxygen in water and sulfur in hydrogen sulfide. It is to be expected that the active acylating agent in the acyl halide-pyridine complex is the positively charged acylium ion, $R-C=O^{\oplus}$, and likewise, that this intermediate should be highly reactive. Equally logical is the conclusion that an acylium ion should be more stable, generally speaking, than the corresponding carbonium ion, since each atom in the acylium ion has a full octet of electrons surrounding it; the presence of pyridine may add somewhat to the stability of the acylium ion also. Hence, the acylium ion might be fairly selective in its reactions, e.g., it might react faster with more nucleophilic atoms, such as oxygen and sulfur, than it would with less nucleophilic amide nitrogen. It is also possible for the acylium ion to produce ketene, by expulsion of a proton in basic solution; in fact, ketenes are commonly synthesized by dehydrohalogenation of acyl chlorides by tertiary amines. If, when the acylium ion is exposed to a nucleophile, expulsion of a proton (promoted by presence of pyridine) occurs before nucleophilic attack, then ketene is formed, which may then be attacked to produce a monoacylated product. Such a monoacylation reaction of primary and

secondary amides has been reported independently by Kocheshkov[16] and Polya.[53]

If, on the other hand, attack by the nucleophile occurs before proton expulsion, or, if the acylium ion is incapable of easily forming ketene via loss of an alpha proton, diacylation might easily occur. Thompson has suggested that diacylation might proceed in two stages, the first being an attack on the amide by one mole of acylating agent to give a short-lived coordination complex of low thermal stability. Loss of hydrogen chloride in the form of pyridine hydrochloride would give the secondary amide. If, however, the complex was more susceptible to a second attack by the acylating agent than the secondary amide, and if its life was sufficiently prolonged (by experimentally mild conditions), another acyl group could then be introduced, giving rise eventually to a tertiary amide.[5] These steps are outlined below.





(16)

Davidson extended the theory of Thompson and suggested actual O-acylation in the first step to form isoimide which, under experimental conditions, undergoes immediate N-acylation to the N-acylisoimide. This compound then rearranges to tertiary amide.[54] This sequence is formulated below.

$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2 + R'COCl \longrightarrow R\text{-}\underset{\underset{OCOR'}{|}}{C}\text{=}NH \xrightarrow{R'COCl}$$

$$R\text{-}\underset{\underset{OCOR'}{|}}{C}\text{=}NCOR' \longrightarrow (RCO)_3N \qquad (17)$$

Since the isoimide would be a stronger base than the original primary amide, it follows that its acylation might be faster than the acylation of the amide, and hence, that the two acyl groups would appear to enter the amide together.[54]

In the case of the variously substituted benzoyl chlorides, and of benzoyl chloride itself, expulsion of an alpha proton is impossible; hence, formation of ketenes is impossible, and diacylation must occur by a path similar to those suggested above. On the other hand, acetyl and propionyl chloride may react by either, or both, of two paths: 1) ketene formation via proton expulsion and subsequent monoacylation, and 2) diacylation, as suggested above. Evidently, the two compounds are attacked faster by oxygen and sulfur than by amide nitrogen, and this attack occurs before ketene formation does; hence, diacylation of water and hydrogen sulfide occurs. Because attack by amide nitrogen is somewhat slower than that of sulfur and oxygen, ketene formation occurs initially, and the ketene then proceeds to give monoacylated product. Such monoacylation of primary and secondary amides has been reported by Kocheshkov.[16]

Cinnamoyl chloride has been observed to participate in both monoacylation and diacylation reactions.[5] This information can be

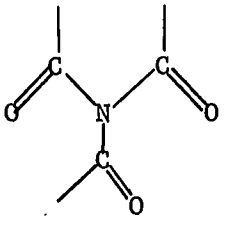
explained that ketene formation, although difficult, is possible, and the acid chloride probably reacts by both of the routes mentioned on the preceding page. Thompson has reported a higher yield of monoacylated amide by cinnamoyl chloride, than that produced by any other acid chlorides capable of diacylation.[5]

It must be mentioned that recent reports of syntheses of tertiary amides by bubbling ammonia through solutions of benzoyl chloride and pyridine at room temperature suggest the possibility of triacylation;[36] however, much more work must be done in this area before definite conclusions can be drawn.

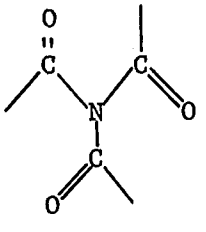
Structure of Tertiary Amides

Much difficulty has been encountered in attempts to answer the intriguing questions concerning the structure of tertiary amides. Several possibilities exist, and infrared and n.m.r. spectral studies have been performed in attempts to elucidate the structure.

In primary amides, the $-\overset{O}{\overset{\|}{C}}-N=$ system is known to be planar.[55] If one assumes a planar (sp^2) nitrogen atom in tertiary amides, then two configurations are possible:



syn

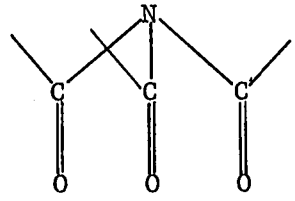


anti

Bell has shown that the n.m.r. spectrum of triacetamide has but a single peak, indicating the equivalency of all the hydrogen atoms.[9] The theory that the three carbonyls of triacetamide are equivalent is supported by a single infrared band in the carbonyl region.[9] Therefore, the anti structure is the correct one--if the nitrogen is in fact sp^2 hybridized. Further support is indicated by steric interference between methyl groups in Dreiding models of triacetamide in the syn configuration.

The reaction of tertiary amides with hydrazine[9,10,36] points out the fact that the tertiary amides cannot assume the syn configuration corresponding to the trans-trans configuration[50] which dibenzamide must clearly favor (see page 36) and which would be highly favorable to the formation of the five-membered triazole ring--a reaction which actually occurs with dibenzamide (see page 31). Hydrazine did not react with triacetamide[9] or tribenzamide[10] to yield cyclic triazoles; instead, hydrazinolysis occurred with both compounds to give the symmetrical diacylhydrazines.[9,10] Similar results were obtained with N-acetyl-dibenzamide; the symmetrical diacetylhydrazine was formed.

A third possibility involves a pyramidal structure (sp^3 nitrogen) which might very properly be called a triacylamine:



In the case of diacetamide, the equivalents of the two planar structures shown above have been isolated and their infrared spectra studied.[50] It has been suggested that the 8° and 78° melting points

reported for triacetamide represent different configurational isomers selected from the three possibilities shown; a similar situation has been reported in that two melting points were obtained for the same tertiary amide.[56] The steric interference in the syn structure would surely make it the least stable, if indeed it can exist at all; but isolation of the anti and pyramidal forms might be possible. This suggestion has not been supported by recent work in this laboratory, where conversion of the 8° form to the 78° material was not effected by heating, cooling, or prolonged standing.[9] The analogous transformation to the higher melting form occurs readily with diacetamide.[50]

A somewhat different structural situation exists for aromatic tertiary amides. Dreiding models of tribenzamide show clearly that the molecule cannot be planar in the syn structure shown above. A planar structure is feasible for the anti structure, though the models show about as much steric interference as is present in the planar configuration of the trityl cation or of benzophenone.[36] Jones has calculated an angel of about 39° between the planes of the benzene rings in benzophenone.[57] Thus, while the planar anti structure may be possible, the syn structure can only exist if the phenyl rings are twisted out of the plane. Maximum pi interaction between the carbonyls and the benzene rings would require rotation about the C-N bond; then, however, there is little reason for the nitrogen atom to be sp^2 hybridized (with a pair of non-bonding electrons in the p-orbital), and it would presumably revert to the sp^3 state.

The structure of mixed aliphatic-aromatic tertiary amides is probably more likely to resemble that of aromatic tertiary amides,

since the steric requirements are similar. The former would be predicted to be more stable than aliphatic tertiary amides because of the presence of two aromatic systems which can participate in resonance interaction with the carbonyl groups.

Primary amides, which are known to be planar,[55] have a carbonyl absorption at 6.0 microns, slightly shifted from the carbonyl peak of tertiary amides,[36] which usually occurs at shorter wavelengths. This leads to the conclusion that the carbonyl group of primary amides does not possess the same characteristics as do the carbonyl groups of tertiary amides. It is possible that this nonequivalence in carbonyl characteristics is brought about by a difference in the stereochemistry of tertiary and primary amides. If this assumption can be made, then it can be said that tertiary amides are not planar, as are primary amides, but are pyramidal.

Like triacetamide, the aromatic tertiary amides having all acyl groups identical which were examined in this laboratory.[10,35,36] show only a single infrared carbonyl absorption. Thus, the carbonyl groups must be symmetrically oriented, and the two structural possibilities for tertiary amides are the planar anti configuration or the pyramidal model. The pyramidal arrangement is favored by observation in this laboratory that tribenzamide has a permanent dipole moment.[58]

Several observations do not support the suggestion that tertiary amides possess a pyramidal structure. It was expected that tertiary amides, having the triacylamine structure, might form quaternary salts as do tertiary amines.[36] However, tribenzamide failed to react with methyl iodide.[36] Had the tertiary amide undergone N-methylation, the

pyramidal structure would have been strongly indicated. Failure to react with methyl iodide does not entirely rule out the pyramidal structure, however, since the nucleophilicity of the nitrogen atom would be strongly diminished even by inductive interactions of the carbonyl groups. p-Bromophenacyl bromide was also heated with tribenzamide in an effort to achieve quaternization of the tertiary amide nitrogen. Only unreacted tribenzamide was recovered.[36]

Another piece of evidence which does not favor the assignment of the triacylamine structure to tertiary amides is the lack of success in reducing tertiary amides to the corresponding amines. In all cases, reduction gave totally unexpected results.[35,36]

Possibly there would be little C=N double bond character in either of the two possible configurations (planar or pyramidal) though the bond order would certainly be higher in the planar molecule than in the pyramidal structure. Correspondingly, the infrared carbonyl absorption should, and does, appear in the vicinity of that of aldehydes and ketones. All of the tertiary amides thus far investigated in this laboratory show a strong absorption at 1230-1260 cm^{-1},[36] in the region of the "imide III" band assigned by Uno and Machida to C-N-C antisymmetric stretching with a contribution from N-H in-plane deformation.[50] The N-H characteristic absorption contribution is, of course, impossible for the tertiary amides. The characteristic absorption at about 1240 cm^{-1} is almost of necessity a C-N stretching absorption like that observed in the same vicinity for aromatic amines. (See Table II.)

Table II. Infrared Absorbances of Tertiary Amides[59] (cm^{-1})

	C=O	C-N
Triacetamide[a]	1725	1230
N-Benzoylphthalimide[b]	1700-1800[c]	1243,1260
Tribenzamide[b]	1705	1245
3,3',3''-Trimethyl-[d]	1695	1260
4,4',4''-Trimethyl-[b]	1713	1253
4,4',4''-Trimethoxy-[b]	1725	1230
4,4',4''-Trinitro-[b]	1735	1230
4,4',4''-Trichloro-[b]	1705	1240
N-Acetyldibenzamide[b]	1670, 1715	1240
	1730	
N-Acetyldi-p-toluamide[b]	1690, 1705	1245
	1735	
N-Acetyldi-p-anisamide[b]	1690, 1700	1250
	1735	
N-Acetyldi-p-chlorobenzamide[b]	1700	1255
	1735	
N-Acetyldi-m-bromobenzamide[b]	1695	1240
	1724	

(a) Neat liquid; (b) KBr disc; (c) 4 peaks, strongest at 1738 cm^{-1}; (d) Nujol mull.

It has been observed that mixed aliphatic-aromatic tertiary amides show two major carbonyl stretching bands, one for each different acyl group. This information, coupled with the shift in frequency from that observed for primary amides, and with the fact that tertiary amides in which all acyl groups are identical show only one carbonyl band, strongly indicates a pyramidal structure. Also, since all the acyclic tertiary amides studied thus far show the same spectral characteristics, their structures must be closely related; the C-N bonds, for example, must be the same in every case. It is therefore suggested that tertiary amides possess a pyramidal structure and are not coplanar molecules, at least in the cases studied so far. This suggestion is based mainly on physical data such as spectral studies, dipole-moment measurements, and molecular model observations. As was stated, the fact that tertiary amides did not form quaternary nitrogen compounds and were not reduced to tertiary amines does not preclude the possibility that these compounds possess a pyramidal structure. It is possible that these reactions would occur under different experimental conditions.

Attempted Preparation of N-Acetyldipropionamide

Since Bell had unprecedented success in the synthesis of triacetamide *via* reaction of diacetamide with isopropenyl acetate,[9] it was anticipated that this same procedure might be a route to the preparation of other tertiary amides, e.g., N-acetyldipropionamide. Hence, dipropionamide was allowed to react with isopropenyl acetate. Surprisingly, the reaction resulted in the preparation of

N-propionyldiacetamide. It is possible that other products such as triacetamide, N-acetyldipropionamide, and tripropionamide were produced but not isolated. In any case, isolation of N-propionyldiacetamide from such a reaction mixture as described above can only be the result of transacylation occurring during the reaction. Such transacylation reactions are not uncommon in the preparation of mixed acid anhydrides[60,61] and in reactions between amines and amides.[62-65] Kocheshkov has reported transacylation by triacetamide,[29] although no explicit experimental details are given.

One can easily visualize four products from the reaction mentioned above, and even ten products from an attempt to synthesize a tertiary amide with all three acyl groups different; thus, a very serious problem arises in the attempted separation of these extremely similar products. Such a situation is not often encountered, and may be the main reason that such a tertiary amide has yet to be prepared.

Reactions of Acylpyridinium Chloride Complexes

It was reported that benzoylpyridinium chloride directly diacylates benzamide in chloroform at low temperatures; very little monoacylation is observed under these conditions.[5] To test this in our laboratory, the reaction of benzoylpyridinium chloride with dipropionamide at low temperatures was attempted. It was found that no acylation occurred, at least not under those reaction conditions employed. Only unreacted dipropionamide, benzoic acid, and benzoic anhydride were isolated from the reaction, the two latter products

resulting from the work-up procedure. These results lend further support to Thompson's diacylation theory.[5]

The reaction of benzoylpyridinium chloride with formamide was also attempted, also at low temperatures. No tertiary amide was isolated; however, it is likely that such a compound as N-formyldibenzamide might be unstable and might easily have decomposed under the work-up procedure used.

In a test of the ketene-formation theory, methacryloylpyridinium chloride was prepared and allowed to react with benzamide. Since methacryloyl chloride cannot form a ketene, it was anticipated that it might be a good diacylating agent; however, after the reaction had been performed in two different solvents and at three different temperatures, only methacrylic acid and benzamide were recovered. It was thought that the nonreactivity of methacryloyl chloride in diacylation might be correlated with Thompson's observation of diacylation and relative acidity of the carboxylic acids corresponding to the acyl halides employed.[5] He found a certain optimum range of acid strengths for carboxylic acids corresponding to the acyl halides, and this range was observed to be defined by ionization constants between 3.38×10^{-5} and 15.4×10^{-5}. Since the ionization constant for methacrylic acid is 2.2×10^{-5},[66] it lies somewhat below the optimum value for diacylation; on the basis of ionization constants, methacryloyl chloride would not be expected to undergo diacylation reactions. Methacryloylpyridinium chloride was reacted with aniline at low temperatures, and only monoacylated product was isolated. In contradiction to this information is a report of the

preparation of trimethacrylamide[18] by the Thompson reaction.[5] It would seem that a re-investigation of the system is in order.

In order to investigate the importance of using chloroform as a solvent in low temperature diacylation, Thompson's reaction of benzoylpyridinium chloride with benzamide to produce tribenzamide[5] was repeated, except that anhydrous ether was used as the solvent instead of chloroform. No tertiary amide was formed, and ethyl benzoate was produced in 70% yield as a result of ethanol addition at the end of the reaction period. Unreacted benzamide was recovered to the extent of 27%; thus 97% of the starting material was accounted for. From these results, it would seem that the use of chloroform as solvent is very important to the success of the diacylation reaction; there is no reaction whatsoever in anhydrous ether, possibly because of solubility factors.

Reactions of Tertiary Amides

Generally speaking, tertiary amides seem to react similarly to primary and secondary amides, with some marked exceptions. Hydrolysis and ammonolysis proceed remarkably repidly in some cases; qualitatively, at least, the hydrolysis of triacetamide proceeds as rapidly in neutral solution as does the hydrolysis of acetic anhydride, and is very much faster in the presence of a trace of acid.[9] Propionyldiacetamide proceeds readily to yield dipropionamide upon exposure to the atmosphere. It is not surprising that triacetamide and N-propionyldiacetamide should be more reactive toward nucleophiles than are acetamide, propionamide, or the corresponding

secondary amides, because of the greater electrophilicity of the carbonyl carbons in the tertiary amides, the steric requirements about the nitrogen atom, and the relative acidities of the leaving groups in the separate cases. However, N-acetylphthalimide reportedly can be recrystallized successfully from boiling water.[67] It is difficult to see why such a compound would not be hydrolyzed at the N-acetyl bond even more readily than is triacetamide. Actually, prolonged digestion with boiling water opens the imide ring to form N-acetylphthalamic acid,[66] rather than attacking the acetyl group. Angle strain in the imide ring may account for the observed reaction path.

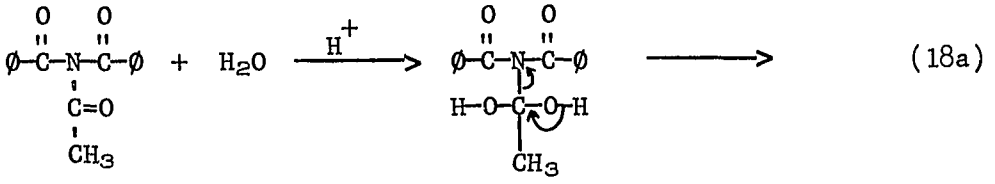
Of further interest is the fact that neither tribenzamide[36] nor N-acetyldibenzamide is readily affected by boiling water. In addition, Thompson, in the course of his preparations, extracted chloroform solutions of various aromatic tertiary amides with 1 M hydrochloric acid and 0.5 M sodium hydroxide, apparently without extensive hydrolysis of the tertiary amides.[5]

The tertiary amide system should, and does, show interesting results when reacted with various reagents. A survey of some reactions of N-acetyldibenzamide as a representative tertiary amide includes those in the following sections.

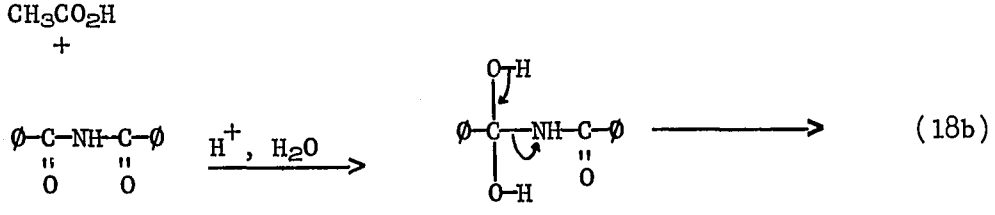
Hydrolysis of N-Acetyldibenzamide

Bell has previously reported the hydrolysis of triacetamide to yield acetic acid.[9] The hydrolysis of N-acetyldibenzamide requires more drastic conditions, and the products are a mixture of dibenzamide, benzamide, and benzoic acid. Presumably, acetic acid was also formed, but in such small quantities that it was not isolated.

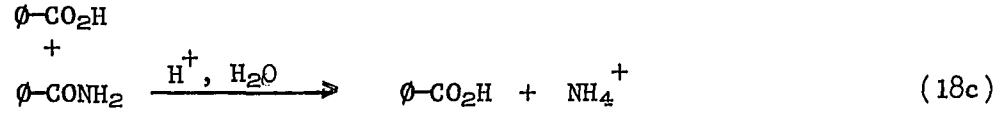
The amount of dibenzamide formed depends on the length of time allowed for the reaction; after 50 hours at room temperature, no dibenzamide is detected. It is interesting to note that no N-acetylbenzamide was isolated in any of the reactions cited in this dissertation; this fact suggests that N-acetylbenzamide is less stable than the parent tertiary amide. The suggested hydrolysis mechanism consists of nucleophilic attack by water on the carbonyl carbon of the acetyl group, followed by cleavage and formation of acetic acid and dibenzamide. Subsequent attack by water at a carbonyl of dibenzamide occurs, accounting for the disappearance of dibenzamide upon prolonged reaction, to form benzoic acid and benzamide. Probably the benzamide is also hydrolyzed to some extent to give more benzoic acid. The overall reaction is formulated below.



(18a)



(18b)

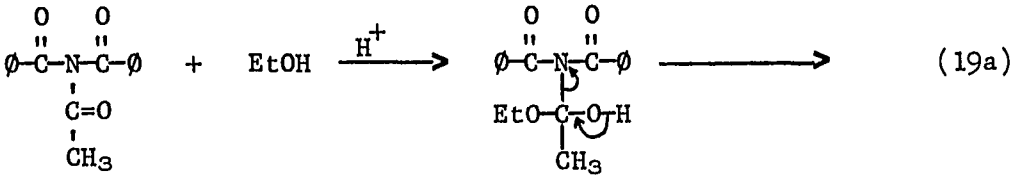


(18c)

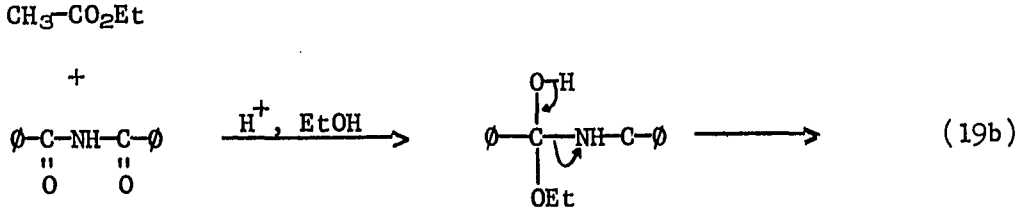
Alcoholysis of N-Acetyldibenzamide

Cowart and Ieyoub have reported the alcoholysis of 4,4',4"-trichlorotribenzamide[35] and tribenzamide,[36] respectively, to give the expected esters and primary amides, contaminated by small amounts of the secondary amides.

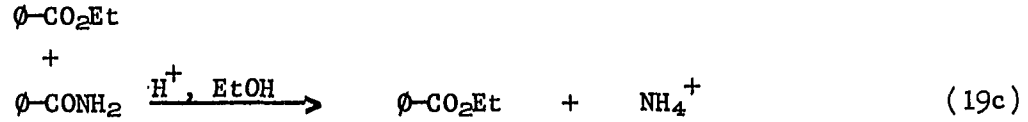
Similar results were obtained when N-acetyldibenzamide was reacted with ethanol, using sulfuric acid as a catalyst; the products were benzamide and ethyl benzoate (the highly volatile ethyl acetate, probably formed in small amounts, was not isolated). The suggested mechanism consists of nucleophilic attack by ethanol at the acetyl carbonyl, followed by cleavage and formation of the ester and secondary amide. Subsequent attack by ethanol at one of the secondary amide carbonyls takes place, and ethyl benzoate is produced. This sequence is shown below.



(19a)



(19b)



(19c)

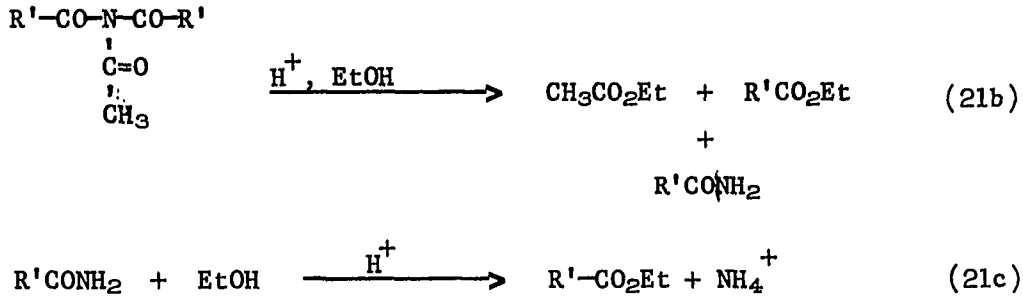
Reaction of Tertiary Amides with Acid Chlorides

In 1967, Ieyoub reported the reaction of tribenzamide and benzoyl chloride to yield dibenzamide and the corresponding acid, benzoic acid, both in low yields.[36] It was speculated that the reaction was similar to one reported by Adams and Vollweiler, in which reaction between aldehydes and acid chlorides was reported to yield a product with the structure shown below.[68]

$$R\text{-}CO\text{-}Cl + R'\text{-}CHO \longrightarrow R'\text{-}\underset{\displaystyle Cl}{\underset{|}{CH}}\text{-}O\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}R \qquad (20)$$

In the case of N-acetyldibenzamide and acid chlorides, and of N-acetyldi-p-toluamide and acid chlorides, only primary amide corresponding to the aroyl group of the tertiary amide and ethyl benzoate were produced. Ester formation was a result of ethanol addition at the end of the reaction period in order to preclude the possibility of hydrolysis of the acid chloride to give misleading products. Formation of the primary amide products can only be formulated by assuming that no reaction occurred between tertiary amide and acid chloride. Addition of ethanol gave rise to ester formation with subsequent liberation of hydrogen chloride. The acid thus formed then catalyzed the reaction between the excess ethanol and tertiary amide to yield primary amide and additional ester. These reactions are shown in the following sequence.

$$R\text{-}CO\text{-}Cl + EtOH \longrightarrow R\text{-}CO_2Et + HCl \qquad (21a)$$

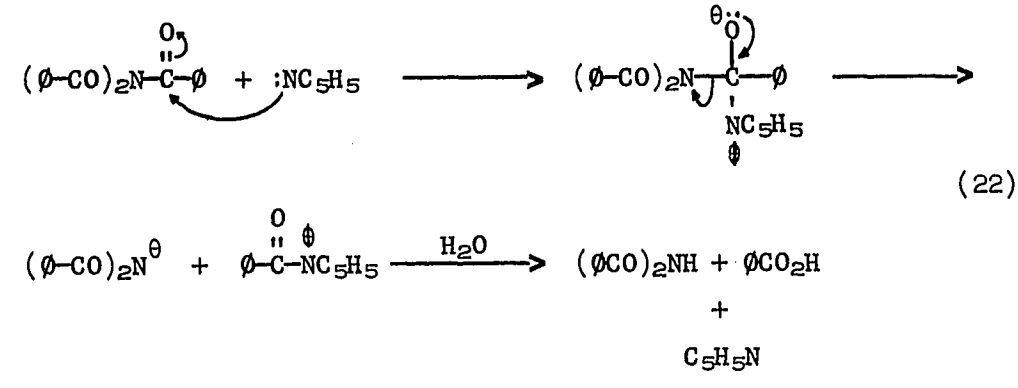


(21b)

(21c)

Reactions of Tertiary Amides with Amines

Prior investigation in this laboratory has indicated a reaction between tribenzamide and pyridine to yield the corresponding secondary amide and carboxylic acid.[36] It was speculated that the following reaction occurred.[36]



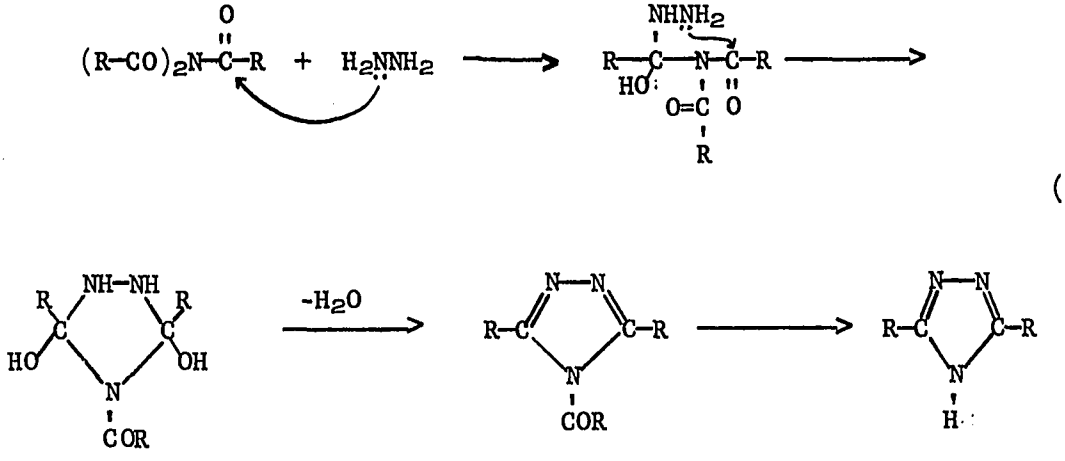
(22)

When N-acetyldibenzamide was refluxed in pyridine, no pure product could be obtained; only brown oil formed which could not be distilled. It appears that the compound decomposed to a resinous tar at reflux temperatures.

Other amines reacted with N-acetyldibenzamide to give N-substituted benzamides and acetamides; this reaction was observed

when benzylamine and ethylamine were the nucleophilic agents employed. This information agrees well with previous investigations in this laboratory,[10,35] and indicates the acylating properties of tertiary amides.

Previous investigations have shown that when hydrazine hydrate was added to tertiary amides which were partially dissolved in hot ethanol, the symmetrical diaroylhydrazines were produced.[10,35] It was anticipated[36] that these reagents would react in a manner analogous to that involved in the reaction of secondary amides with hydrazine to yield 3,5-disubstituted-1,2,4-triazoles.[46] Triazole formation was suggested to occur according to the following equation.[36]

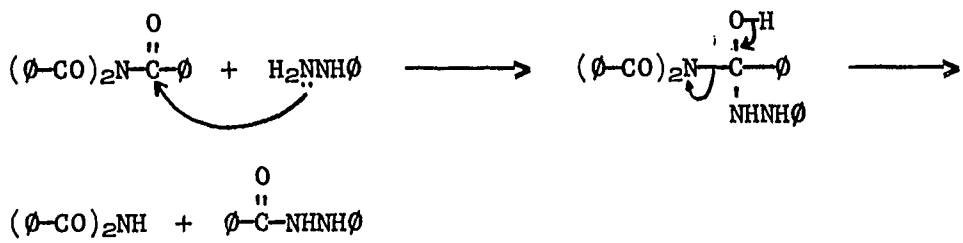


(23)

However, it is not surprising that the above reaction did not occur, since tertiary amides cannot assume the <u>syn</u> planar conformation; hence, their carbonyl groups are not positioned so as to favor formation of the five-membered ring. Hydrazinolysis is also favored by the fact

that tertiary amides are more reactive toward nucleophilic displacement than are secondary amides. N-Acetyldibenzamide reacted as expected to produce the diacetylhydrazine, the same product as that from the triacetamide reaction. Hence, the acetyl group seems to be the preferred acyl group in the acylation of hydrazine. The fact that the reaction must occur in two steps is indicated, since two tertiary amide molecules are involved per molecule of hydrazine. Another possible explanation for obtaining the diacetylhydrazine would involve a termolecular mechanism. The present investigation did not distinguish between the two possibilities.

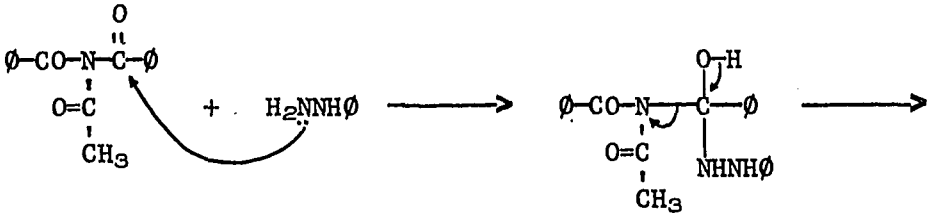
A reaction between tribenzamide and phenylhydrazine has been reported to yield benzoic acid phenylhydrazide by the following mechanism:[36]

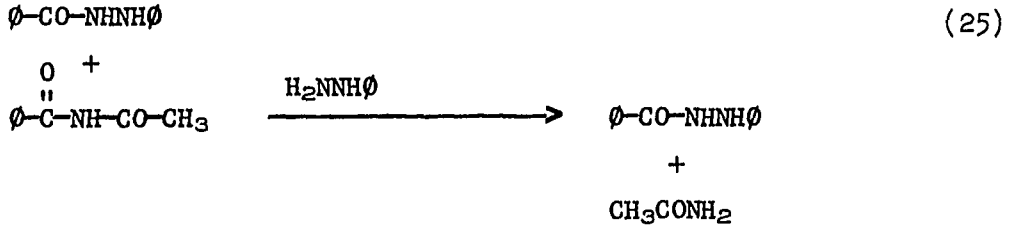


(24)

Similar results were obtained when N-acetyldibenzamide and phenylhydrazine were reacted. The only isolated product was benzoic acid phenylhydrazide. Why this reaction should give a benzoylated product is not understood, in light of the contradictory results from the above reaction. However, the formation of an oil which could not be purified may have obscured detection of other products. It is possible that benzoic acid phenylhydrazide was a product from a side reaction, since the yield was low. Repeated

attempts to detect other products were unsuccessful. In order to formulate formation of the product isolated, expected nucleophilic attack must occur at the carbonyl carbon of one of the benzoyl groups, with subsequent cleavage resulting in the formation of N-acetylbenzamide and benzoic acid phenylhydrazide. Attack by a second molecule of phenylhydrazine at the carbonyl of the benzoyl group could then produce another molecule of benzoic acid phenylhydrazide and acetamide. This reaction is shown below.





(25)

Pyrolysis of N-Acetyldi-p-toluamide

Curtius reported in 1890 that tribenzamide sublimed undecomposed.[3] Work in this laboratory has disclosed that tribenzamide, after being melted, vaporized, and allowed to condense, yields benzonitrile and an unidentified product.[36] When the reaction was carried out in vacuo, only benzonitrile was obtained.[36] Pyrolysis of N-acetyldibenzamide produced benzonitrile, and brown char.

Probably some acetonitrile was also produced, but was not detected with the procedure used. Thus, pyrolysis of tertiary amides seems to proceed in the same manner as that of primary amides to give nitriles.

Reaction with Sulfuric Acid

Ieyoub, in 1967, allowed tribenzamide to react with sulfuric acid with the anticipation that the tertiary amide might be protonated to form the ammonium salt. However, the only product reported was benzoic acid.[36] Reaction of N-acetyldi-p-toluamide proceeds similarly to give p-toluic acid. Again, the high susceptibility of the carbonyl carbons of tertiary amides to nucleophilic attack is demonstrated. Instead of simple protonation occurring, the sulfate anion attacked the carbonyl carbons to produce p-toluic acid and probably acetic acid although none was isolated. Thus the reaction is similar to one reported by Tyka between tribenzoylphosphine and sulfuric acid,[29] shown below.

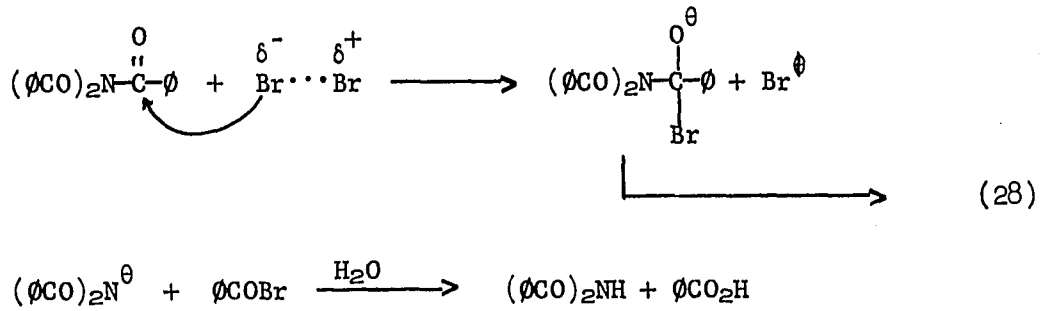
$$(\text{Ø-CO})_3\text{P} + 3\ \text{H}_2\text{SO}_4 \longrightarrow \text{PH}_3 + 3\ \text{ØCO}_2\text{SO}_3\text{H} \xrightarrow{\text{H}_2\text{O}} 3\ \text{ØCO}_2\text{H} + 3\ \text{H}_2\text{SO}_4 \qquad (26)$$

Reaction with Bromine

Tyka, in 1963, reported a reaction in which bromine was allowed to react with tribenzoylphosphine to yield benzoyl bromide and phosphorus tribromide.[29]

$$(\text{ØCO})_3\text{P} + 3\ \text{Br}_2 \longrightarrow 3\ \text{ØCOBr} + \text{PBr}_3 \qquad (27)$$

In a similar reaction with tertiary amides, electrophilic attack of bromine on the benzene rings was not expected, and indeed did not occur. Instead, cleavage occurred after the initial attack by bromine, and the end products from tribenzamide were benzoic acid and dibenzamide.[36] Thus, the reaction was similar to that of Tyka,[29] except that the tertiary amide reaction did not proceed so far as did that of tribenzoylphosphine. Presumably, one of the tribenzamide carbonyl carbons was attacked by the relatively negative portion of the polarized bromine molecule; and cleavage of the molecule followed, producing dibenzamide and benzoyl bromide, which was subsequently hydrolyzed to benzoic acid.[36]



(28)

The reaction between N-acetyldibenzamide and bromine resulted only in the formation of a brown oil, which darkened and became a brown tar upon attempted distillation. Presumably, the presence of the acetyl group made the molecule even more susceptible to nucleophilic attack, and perhaps even subsequent decomposition.

Friedel-Crafts Reaction

It is to be expected that tertiary amides might serve as excellent acylating agents because of the fact that loss of an acyl or

aroyl group would relieve steric interference about the nitrogen atom in the tertiary amide molecule. Kocheshkov reported that triacetamide easily acylates a number of representative compounds and that any one of the three acyl groups would participate in acetylation reactions.[16] He also stated that tertiary amides would undergo transacylation reactions.[16]

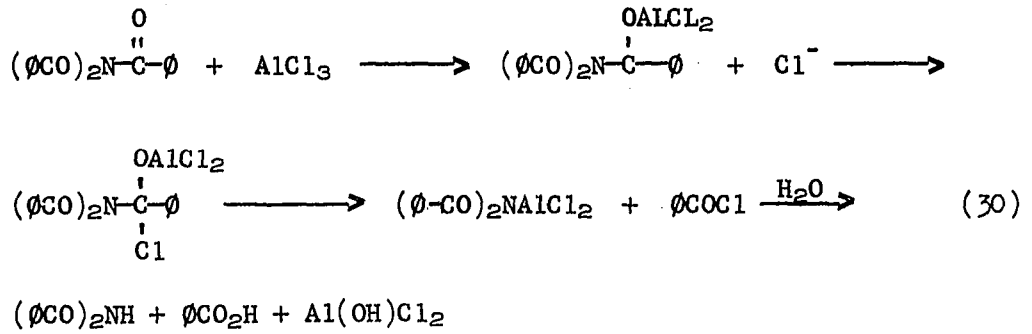
Tyka has reported the use of tertiary amides in Friedel-Crafts acylation and aroylation of benzene. He reported that the reaction of tribenzamide with benzene under Friedel-Crafts reaction conditions yields benzophenone, and that of N-acetyldibenzamide yields acetophenone.[29] He also obtained benzophenone by the reaction of tribenzoylphosphine and benzene using aluminum chloride as the catalyst.[29] The following mechanism was proposed:[29]

$$(\phi CO)_3P + AlCl_3 \longrightarrow \left[(\phi CO)_3P\rightarrow AlCl_3\right] \longrightarrow$$

$$\phi-\overset{O}{\overset{\|}{C}}\phi + \left[(\phi CO)_2P\rightarrow AlCl_3\right]^{\theta} \xrightarrow{H^+} (\phi CO)_2PH + AlCl_3 \quad (29)$$

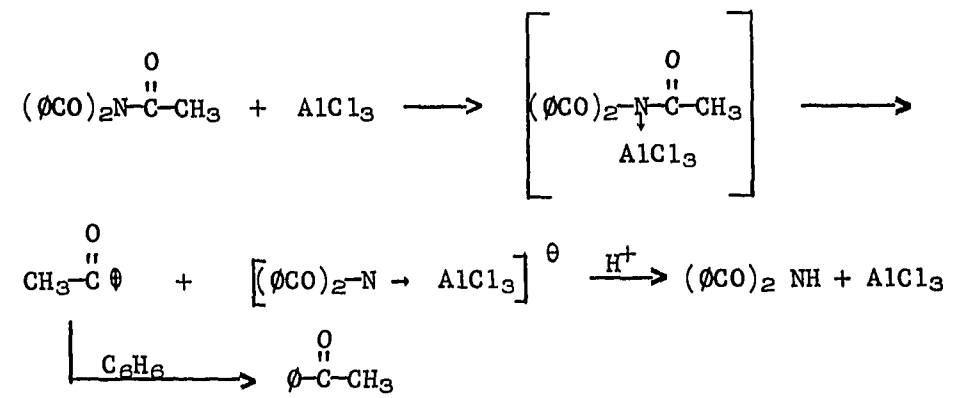
$$\downarrow C_6H_6 \longrightarrow \phi-CO-\phi$$

Earlier investigations in this laboratory achieved no success in attempts to benzoylate benzene using tribenzamide as the aroylating agent,[36] as Tyka did.[29] These discrepancies may be the result of subtle differences existing in the two different experimental methods. The reaction of tribenzamide, benzene, and aluminum chloride produced only benzoic acid, and was explained by the following mechanism.[36]



(30)

These differences prompted a reinvestigation of the N-acetyldibenzamide system in Friedel-Crafts acylation of benzene. The findings of this investigation substantiated those of Tyka[29] in that acetylation of benzene occurred. Acetophenone and dibenzamide were the products obtained from the reaction of N-acetyldibenzamide. Based on Tyka's work,[29] the following mechanism is proposed:

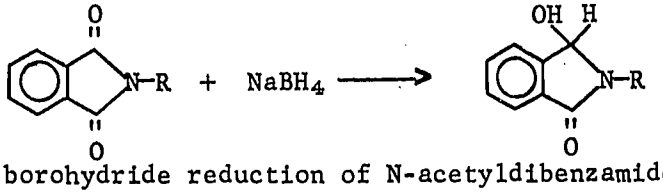


Reduction of Tertiary Amides

As was expected by the results from previous work in this laboratory,[36,37] reduction of N-acetyldibenzamide to the corresponding tertiary amine was not achieved. Usual reduction methods such as sodium in alcohol and zinc amalgam-hydrochloric acid (Clemmensen

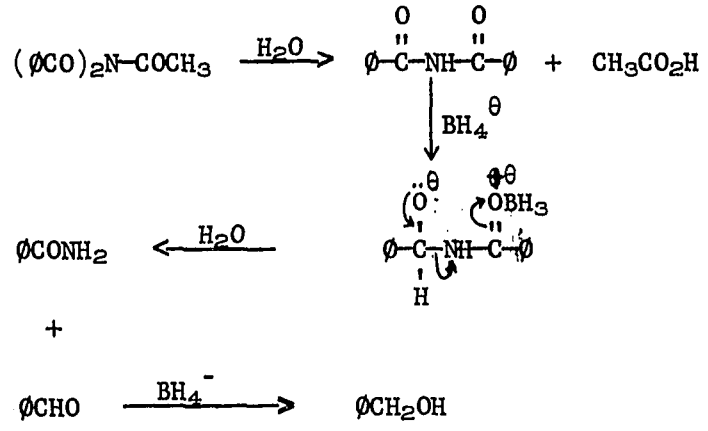
reduction) have been reported to cleave the tertiary amides before reduction occurs.[36,37] Sodium reduction of tribenzamide produced benzamide and ethyl benzoate, and benzoic acid and dibenzamide were obtained from the attempted Clemmensen reduction.[36] These products were rationalized by assuming an attack on the carbonyl carbon by ethoxide ion, in the case of the sodium in alcohol reduction, and by an attack on the carbonyl carbon by the chloride ion in the Clemmensen reduction attempt.[36] No reaction whatsoever occurred when catalytic hydrogenation of tribenzamide was attempted.[36] Clemmensen reduction of N-acetyldibenzamide only produced benzamide; evidently hydrolysis was the major reaction, instead of reduction.

Diborane and sodium borohydride were employed as reducing agents for tribenzamide[36] and 4,4',4"-trichlorotribenzamide,[35] with similar results. N-Substituted alkylbenzamides were obtained in both cases, and benzyl alcohol was obtained from tribenzamide.[36] It might be anticipated that sodium borohydride reduction would result in a reaction similar to that reported by Horu in which sodium borohydride was used to reduce phthalimides to hydroxyphthalimidines, as follows.[44]



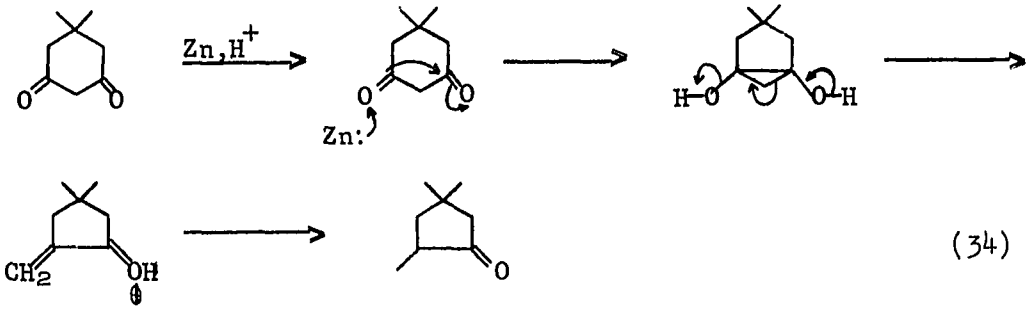
(32)

Sodium borohydride reduction of N-acetyldibenzamide resulted in the formation of benzyl alcohol and benzamide. No product similar to that from the phthalimide reduction could be isolated. The following mechanism is proposed, assuming that hydrolysis of the acetyl group to acetic acid proceeds before reduction.



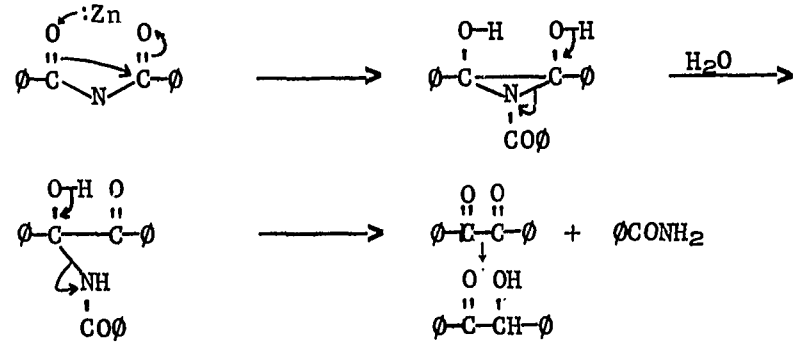
(33)

Other reduction investigations using zinc and acetic acid to reduce tribenzamide were performed,[36] with the anticipation that the reduction might proceed in a manner analogous to that described by Brewster, who performed the following reaction.[69]



(34)

Application of an analogous mechanism to the tribenzamide reduction permits the prediction of the following reaction sequence:[36]



(35)

The product obtained seemed to be impure N-benzylbenzamide, and it was speculated that perhaps benzil or benzoin was produced in small yields by the mechanism suggested above, although no conclusive evidence was obtained.[36] The similar reduction of N-acetyldibenzamide produced N-benzylbenzamide and benzamide. It would seem that hydrolysis of the tertiary amide prior to actual reduction occurred, as it did in the sodium borohydride reduction (see equation 33). Evidently, hydrolysis of both the acetyl groups and the benzoyl group occurred, and subsequent reduction of dibenzamide produced N-benzylbenzamide.

EXPERIMENTAL PART

Attempted Preparation of N-Acetyldipropionamide

Dipropropionamide was prepared according to the method of Davidson and Skovronek.[54] Freshly distilled propionic anhydride (74.3 g., 0.57 mole) was added to 35.4 g. of propionamide (0.5 mole) in a 250 ml. round-bottomed flask fitted with a Friedrich cold water condenser; 2 drops of propionyl chloride was added, and the solution was refluxed for 1/2 hour. Solvent was then distilled from the reaction mixture, leaving white solid. The solid residue was recrystallized from 95% ethanol to give 11.65 g. of dipropionamide, m.p. 154-155° (lit.[5] 154°). The yield was 18%.

To 6.45 g. of dipropionamide (0.05 mole) in a 100 ml. round-bottomed flask was added 40 ml. of isopropenyl acetate (freshly distilled) and 3 drops of concentrated sulfuric acid. The reaction flask was fitted with a Dean-Stark trap to which a cold water condenser was connected, and the solution was refluxed for about 2 1/2 hours. During this time, acetone was distilled from the reaction vessel, collected in the Dean-Stark trap, and identified by its infrared spectrum and the melting point of its 2,4-dinitrophenylhydrazone (m.p. 121-124°; lit.[4] 126°). At the end of the reaction period, solvent was distilled from the reaction vessel until the reaction solution was reduced to a small volume; the high-boiling residue was distilled under vacuum, using a short fractionating column filled with glass beads. Two fractions were collected, a

liquid at 52-57° (4 mm. Hg) and a solid, m.p. 148-152°, at 109-112° (5.5 mm. Hg). The solid was identified as unreacted dipropionamide, and the liquid was identified as N-propionyldiacetamide by its infrared spectrum, elemental analysis,[70] and n.m.r. spectrum.[71]

Calc. for $C_7H_{11}NO_3$	C 53.50	H 7.00	N 8.92
Found for "	C 54.01	H 7.09	N 8.94

(average of two determinations)

n.m.r. data:	Relative Area	Tau
	3	8.9 (triplet)
	6	7.7 (singlet)
	2	7.3 (quartet)

Reactions of Acylpyridinium Chloride Complexes

(1) Twenty ml. of anhydrous pyridine in 100 ml. of anhydrous ether was cooled to -30° in a 4-neck 300 ml. round-bottomed flask fitted with dropping funnel, drying tube, stirrer, and thermometer. Fifteen ml. of benzoyl chloride in 50 ml. of anhydrous ether was added slowly with stirring. A finely-divided white solid appeared immediately and the solution was stirred for fifteen minutes after addition of benzoyl chloride was completed. The solution was filtered immediately, with exclusion of the atmosphere, but the white solid was extremely hygroscopic and could not be purified.

(2) Twelve ml. of benzoyl chloride in 50 ml. of anhydrous ether was cooled to -70° in a 4-neck 500 ml. round-bottomed flask fitted with dropping funnel, drying tube, stirrer, and thermometer.

Anhydrous pyridine (16.3 ml.) in 50 ml. of anhydrous ether was added slowly, with stirring; the temperature rose approximately 10° with the addition, and the solution was cooled again to -70°. Dipropionamide (13 g.) suspended in 200 ml. of anhydrous ether was added to the mixture, which already contained a white, finely-divided solid. The solution was stirred for fifteen additional minutes, and then was allowed to warm to room temperature. The remaining solid was collected by vacuum filtration and washed twice with 20-ml. portions of 1 M hydrochloric acid; it was recrystallized from acetone and ether to give 7.3 g. of unreacted dipropionamide. The ether filtrate was washed twice each with 60-ml. portions of 1 M hydrochloric acid, 0.5 M sodium hydroxide, and distilled water; upon evaporation, the ether filtrate yielded 2.2 g. of benzoic anhydride. The basic extract was neutralized with concentrated hydrochloric acid and gave 0.9 g. of benzoic acid. No other products were found upon evaporation of all aqueous extracts.

(3) Benzoyl chloride (12 ml., 0.1 mole) in 50 ml. of anhydrous ether was cooled to -70° in a 4-neck 300 ml. round-bottomed flask fitted with a dropping funnel, drying tube, stirrer, and thermometer. Dry pyridine (16.3 ml., 0.2 mole) in 50 ml. of anhydrous ether was added slowly, with stirring, and again a temperature rise was observed. After the flask had been cooled again to -70°, 4 ml. of formamide in 25 ml. of anhydrous ether was added to the mixture, which already contained white solid. The reaction mixture was stirred for 4 hours, and then was allowed to warm to room temperature. No solid remained when the solution reached room temperature. The ether

solution was evaporated, leaving a yellow oil, which was found to be water soluble. No solid products were obtained.

(4) Methacryloyl chloride was prepared by reacting 43 g. of methacrylic acid (0.5 mole) in 39.5 g. of pyridine with 106 g. of benzenesulfonylchloride (0.6 mole). The initial pyridine solution was cooled in an ice bath before addition of the benzenesulfonylchloride. After the initial heat of reaction was dissipated, the solution was distilled through a vacuum-jacketed Vigreaux column. Methacryloyl chloride was collected at 98-100° in 53% yield (27.6 g.).

A solution of freshly prepared methacryloyl chloride (20.9 g., 0.2 mole) in 100 ml. of anhydrous ether was cooled to -70° in a 4-neck 300 ml. round-bottomed flask fitted with a dropping funnel, drying tube, stirrer, and thermometer. A solution of 16.3 g. of pyridine (0.2 mole) in 50 ml. of anhydrous ether was added slowly with stirring; heat was generated and a white solid appeared in the reaction flask. The solution took on an orange color. After the mixture had been cooled again, solid benzamide (11 g. 0.09 mole) was added, and the mixture was stirred for 20 hours at -70°, after which time stirring was discontinued and the solution was allowed to warm to room temperature. The remaining white solid was collected by vacuum filtration, and was found to be water soluble. The ether filtrate was extracted with 25-ml. portions of 0.5 M sodium hydroxide until no heat was generated by the extraction process. The ether portion and the aqueous extract both took on a yellow-green color. Evaporation of the ether filtrate left no residue. An aqueous solution of the white solid collected above was added to the

sodium hydroxide extract, and the resulting solution was distilled. The non-aqueous distillate was collected at 151-154°, and was identified as methacrylic acid by its infrared spectrum.

(5) The previous reaction was repeated, using chloroform as solvent. No solid was left in the reaction mixture after it was allowed to warm to room temperature. The chloroform solution was extracted twice each with 60-ml. portions of 1 M hydrochloric acid, 0.5 M sodium hydroxide, and distilled water. Evaporation of the chloroform solution on a steam cone left a solid which was found to be benzamide. Neutralization of the sodium hydroxide extract gave no solid product, and distillation yielded only methacrylic acid. Evaporation of the other aqueous solutions yielded only benzamide.

(6) The previous reaction was repeated, at -40°; no satisfactory results were obtained.

(7) The same reaction was performed once more at room temperature. Again, no satisfactory results were obtained.

(8) Freshly prepared methacryloyl chloride (20.90 g., 0.2 mole) in 75 ml. of chloroform and 25 ml. of methylene chloride was cooled to -70° in a 4-neck 300 ml. round-bottomed flask fitted with dropping funnel, drying tube, stirrer, and thermometer. Pyridine (16.3 ml., 0.2 mole) in 50 ml. of chloroform was added, and the solution was again cooled to -70°. Aniline was added (9.3 g., 0.1 mole) slowly, with stirring, and the stirring was maintained for 21 hours at -70°. The chloroform was evaporated from the solution on a steam cone, leaving white solid. The solid was

recrystallized from ethanol and water to give a melting point of 84-86°. The product was identified as methacrylanilide (lit.[72] m.p. 87°) by comparing its infrared spectrum with that of the known compound. No other product was isolated.

(9) Benzoyl chloride (28.1 g., 0.2 mole) in 100 ml. of anhydrous ether was cooled to -70° in a 4-neck 300 ml. round-bottomed flask fitted with a dropping funnel, drying tube, stirrer, and thermometer. Pyridine (16.3 g., 0.2 mole) in 50 ml. of anhydrous ether was added slowly with stirring, and the solution was again cooled to -70°. Benzamide was added (12.1 g., 0.1 mole), and stirring was maintained at -70° for 20 hours, at which time 50 ml. of absolute ethanol was added; and the solution was allowed to warm to room temperature. The solution was extracted twice each with 60 ml. portions of 1 M hydrochloric acid, 0.5 M sodium hydroxide, and distilled water. Evaporation of the chloroform on a steam cone left a high-boiling liquid which was distilled; the major portion of distillate was collected at 205-209°, and was subsequently identified as ethyl benzoate on the basis of its boiling range and infrared spectrum. Ethyl benzoate was produced in 70% yield (21.1 g.). The only other material isolated was 6.5 g. of benzamide (0.54 mole). The recovery was 27%; thus 97% of starting material was accounted for.

Preparation of Mixed Aromatic-Aliphatic Tertiary Amides

N-Acetyldibenzamide. All mixed aromatic-aliphatic tertiary amides mentioned in this dissertation were prepared by the method of Thompson.[5] In this preparation, a solution of 42.18 g. of benzoyl

chloride (0.3 mole) in 300 ml. of chloroform and 96 ml. of methylene chloride was cooled to -70°. The reaction vessel was a 4-neck 500 ml. round-bottomed flask fitted with a drying tube, stirrer, dropping funnel, and thermometer. Pyridine (30 ml.) which had been previously dried by refluxing over barium dioxide was added, with generation of heat and appearance of finely-divided white solid. After the mixture was cooled again, finely-powdered acetamide (16.8 g., 0.3 mole) was added, and stirring was continued for 4 hours, with the temperature being maintained at -70°. At the end of the reaction period 30 ml. of absolute ethanol was added, and the reaction mixture was allowed to warm to room temperature. The chloroform solution was then extracted twice with 360-ml. portions of cold 1 M hydrochloric acid, and once each with similar portions of 0.5 M sodium hydroxide and distilled water. The chloroform was evaporated on a steam cone with the aid of a stream of air, and the remaining oil was cooled and allowed to crystallize. The tertiary amide, obtained in approximately 66% yield, was recrystallized from carbon tetrachloride and petroleum ether (b.p. 60-68°). The melting point was 84-85° (lit.[5] 84.5-85.5°).

N-Acetyldi-p-toluamide. Essentially the same procedure as above was followed, with a yield of 60%, m.p. 153-155° (lit.[5] 156.1-156.8°).

N-Acetyldi-p-chlorobenzamide. The same procedure was followed here as above except that the following amounts were used: 13.1 g. p-chlorobenzoyl chloride (0.075 mole), 15 ml. of pyridine, and 5.31 g. acetamide (0.09 mole). The yield was 29%, m.p. 158-160° (lit.[5] 162-163°).

N-Acetyldi-m-bromobenzamide. m-Bromobenzoyl chloride was prepared by reaction of 50.25 g. of m-bromobenzoic acid (0.25 mole) with thionyl chloride (120 ml.), under reflux for three hours. Thionyl chloride was distilled from the reaction mixture, and the residue was vacuum distilled to give m-bromobenzoyl chloride, b.p. 96° (1.5 mm. Hg) (lit.[72] 119-122°, 13 mm. Hg). The tertiary amide was prepared by the same procedure used for the preceding tertiary amide, and the yield was 71%, m.p. 127-129° (lit.[5] 129.4-130°).

N-Acetyldianisamide. A solution of 25.4 g. of anisoyl chloride (0.15 mole) in 150 ml. of pyridine was cooled to 0°, and 8.85 g. of acetamide (0.15 mole) was added. After maintaining stirring for three hours at 0°, 15 ml. of absolute ethanol was added, and the mixture was poured into 105 ml. of cold 3 M hydrochloric acid. The resulting solid was separated by vacuum filtration and stirred with two 150-ml. portions of 0.5 M sodium hydroxide. The remaining 3 g. of solid was filtered out and purified by dissolving it in 42 ml. of methanol containing 0.75 g. of glycine and 40 drops of pyridine. After the solution was boiled for 20 minutes, it was poured into 225 ml. of cold 0.5 M sodium hydroxide. The insoluble tertiary amide was extracted with ether and recrystallized from ether and petroleum ether (b.p. 60-68°). The yield was 0.5 g., m.p. 106-108° (lit.[5] 107.8-108.2°).

Reactions of Tertiary Amides

Hydrolysis. N-Acetyldibenzamide (5.0 g.) was dissolved in 150 ml. of tetrahydrofuran, and a solution of 125 ml. of distilled

water and 25 ml. concentrated hydrochloric acid was added. The solution was stirred at room temperature, and 100 ml. portions were withdrawn at time intervals of 28 hours, 50 hours, and 71 hours. Each portion was evaporated to dryness at room temperature, and the residue was recrystallized from 95% ethanol and water. The following products were obtained:

28 hours	benzamide	.43 g.
	benzoic acid	.46 g.
	dibenzamide	.07 g.
50 hours	benzamide	.58 g.
	benzoic acid	.44 g.
71 hours	benzamide	.68 g.
	benzoic acid	.38 g.

The products were identified by their melting points and infrared spectra.

Alcoholysis. In a 500 ml. one-neck round-bottomed flask were placed 2.7 g. of N-acetyldibenzamide (0.01 mole), 250 ml. of absolute ethanol, and 3 drops of concentrated sulfuric acid. A Friedrich cold-water condenser was attached, and the solution was refluxed for 23 hours. The ethanol was removed by distillation, leaving white solid; the solid was separated by vacuum filtration, and the filtrate was distilled. The distillate was identified as ethyl benzoate on the basis of its boiling point (210-213°) and its infrared spectrum.

The solid was recrystallized from hot water and was identified as benzamide by its melting point (127-129°) and infrared spectrum. The yield was 1.51 g., 60%.

Reaction with Acid Chlorides. In a 125 ml. Erlenmeyer flask was placed 2.7 g. of N-acetyldibenzamide (0.01 mole); 50 ml. of chloroform was added. To this solution was added 1.2 ml. of benzoyl chloride (0.01 mole), and a drying tube was fitted onto the flask. The solution was allowed to stand at room temperature for a period of 7 days, and then 2 ml. of absolute ethanol was added. The solution was evaporated to a small volume on a steam cone, and the solid was collected by vacuum filtration. Recrystallization from 95% ethanol produced a product which was identified as benzamide on the basis of its melting point (128-129°) and infrared spectrum. The yield was .83 g., 34%.

The filtrate was identified as ethyl benzoate by its boiling point (208-210°) and infrared spectrum.

The same reaction was performed, using acetyl chloride in place of benzoyl chloride. The product was identified as benzamide by its melting point (130°) and infrared spectrum. The yield was .85 g., 35%.

N-Acetyldi-p-toluamide was reacted with benzoyl chloride and acetyl chloride by the same procedure above. The products are given below.

benzoyl chloride reaction	p-toluamide, .97g.
acetyl chloride reaction	p-toluamide, 1.04g.

Reaction with Benzylamine. In a 150 ml. round-bottomed flask were placed 2.7 g. of N-acetyldiacetamide (0.01 mole), 5.35 g. of benzylamine (0.05 mole), and 75 ml. of chloroform. The solution was refluxed for 22 hours, after which time the chloroform was removed by distillation. A white residue was left, and it was recrystallized from 95% ethanol and water. The white solid was identified as N-benzylbenzamide by its melting point (102-104°) and infrared spectrum. The yield was 2.13 g., 99%.

Further evaporation of the filtrate from above yielded another product, identified as benzamide. The yield was 0.45 g., 37%.

Reaction with Ethylamine. Exactly the same procedure as above was used in this reaction. The products were N-ethylbenzamide (0.25 g., 17%), N-ethylacetamide (.45 g., 52%), and benzamide (.90 g., 74%). The products were identified by their melting or boiling points and their infrared spectra.

Reaction with Phenylhydrazine. N-Acetyldibenzamide (1.6 g., 0.006 mole) was dissolved in 50 ml. of hot absolute ethanol in a 250 ml. Erlenmeyer flask; to this boiling mixture was added 2 ml. of phenylhydrazine. The solution was allowed to continue boiling until almost all of the ethanol had evaporated; it was then allowed to cool to room temperature, and subsequently cooled in an ice bath. A white crystalline solid resulted, and it was recrystallized from 95% ethanol and water to give a solid melting at 167-169°. The material was identified as benzoic acid phenylhydrazide (lit.[72] 171°)

by its melting point and infrared spectrum. The yield was 0.48 g., 38%. Repeated attempts gave no other products.

Reaction with Hydrazine. N-Acetyldibenzamide (5.4 g., 0.02 mole) was dissolved in 60 ml. of tetrahydrofuran. To this solution was added 4 ml. of 85% aqueous hydrazine hydrate. The solution was allowed to boil until most of the solvent had evaporated. The remaining oil was allowed to stand overnight, and a white solid was deposited. The solid was recrystallized from carbon tetrachloride to give a melting point of 137-139°. It was identified as diacetylhydrazide (lit.[72] 140°) on the basis of its melting point and infrared spectrum. The yield was 0.25 g., 22%

Pyrolysis. N-Acetyldibenzamide (2.7 g., 0.010 mole) was placed in a 25 ml. round-bottomed distilling flask; the flask was heated until the tertiary amide melted and began to boil. Heating was continued, and distillate was collected at the side-arm with a test tube immersed in an ice bath. The distillate was identified as benzonitrile on the basis of its boiling point of 190°; (lit.[72] 191°) and infrared spectrum. The infrared spectrum also showed traces of what appeared to be acetonitrile, although none was isolated. The yield of benzonitrile was 1.03 g., 99%. A brown char was left in the bottom of the distilling flask.

Reaction with Sulfuric Acid. N-Acetyldi-p-toluamide (1 g.) was added to 4 ml. of concentrated sulfuric acid in a 25 ml. Erlenmeyer flask, and allowed to stand for 3 days. Water (20 ml.)

was added, resulting in the appearance of white solid. The mixture was vacuum filtered, and the white solid was recrystallized from benzene and petroleum ether (b.p. 60-68°). The product was identified as p-toluic acid on the basis of its melting point of 167-169°; lit.[72] 169°) and its infrared spectrum. The yield was .72 g., 80%.

Reaction with Bromine. In a 100 ml. round-bottomed flask fitted with a Friedrich cold-water condenser was placed 2.7 g. of N-acetyldibenzamide (0.01 mole), 50 ml. of chloroform, and 1 g. of iron powder. This mixture was heated until all of the tertiary amide had dissolved, and after refluxing had ceased, the condenser was removed so that bromine in excess could be introduced into the reaction vessel. The condenser was again fitted onto the flask and a delivery tube was attached to the condenser and extended into a sodium hydroxide trap. The mixture was heated gently for one hour, after which time the flask was placed under the vacuum hood and heated in order to drive off excess bromine.

The chloroform solution was gravity filtered in order to remove the iron powder, and then the chloroform was evaporated. The brown oil which resulted was boiled with petroleum ether (b.p. 60-68°) in an attempt to induce crystallization, but no crystalline product could be obtained. It was then dissolved in acetone, and the solution was boiled with decolorizing carbon; filtration of the mixture produced the same brown color. Distillation caused the oil to darken, and a brown tar was left in the bottom of the distilling flask. No product could be isolated.

Friedel-Crafts Reaction. In a 200 ml. round-bottomed flask fitted with a Friedrich cold-water condenser was placed 5.4 g. of N-acetyldibenzamide (0.02 mole), 50 ml. of sodium-dried, thiophene-free benzene, and 30 g. of aluminum chloride. The mixture was allowed to reflux for one hour, and then cooled in an ice-water bath. Ice (100 g.) was added, bit by bit, and after the reaction of decomposition had subsided, 20 ml. of concentrated hydrochloric acid and 100 ml. of water were added. The mixture was then extracted with 50 ml. of ether, and the ether-benzene portion was evaporated on a steam cone. The residue consisted of an orange oil, to which petroleum ether was added (b.p. 60-68°); this operation caused yellow-orange crystals to separate. The solid was collected by vacuum filtration, and recrystallized from ethanol and water. It was identified as dibenzamide on the basis of its infrared spectrum and melting point of 145-147°;(lit.[5] 148-149°).

The petroleum solution was evaporated to a small volume and then distilled; distillate was collected at 200°, and identified as acetophenone by its infrared spectrum. The yields were: dibenzamide, .75 g., 17%; acetophenone, 1.4 g., 59%.

Reductions

Zinc and Acetic Acid. Zinc dust (6.5 g., 0.1 mole) was placed in a 125 ml. round-bottomed flask, and 50 ml. of glacial acetic acid and 2 ml. of water were added. N-Acetyldibenzamide (2.7 g., 0.01 mole) was added, and a Friedrich cold-water condenser was fitted onto the flask. The mixture was heated for 80 hours, at which time

the solution was gravity-filtered. The filtrate was neutralized with 1 M sodium hydroxide and extracted with ether. The ether was evaporated over a steam cone, leaving a residue of white solid, which was collected by vacuum filtration. The solid was recrystallized from 95% ethanol and water to give .34 g. of a product identified as N-benzylbenzamide on the basis of its melting point (98-100°) and infrared spectrum. Further evaporation of the filtrate gave .24 g. of benzamide. The yields were 23% and 20%, respectively.

Sodium Borohydride. N-Acetyldibenzamide (2.7 g., 0.01 mole) was dissolved in 80 ml. of tetrahydrofuran in a 125 ml. Erlenmeyer flask. This solution was added slowly, with stirring, to a solution of 0.1 g. of sodium hydroxide and 0.5 g. of sodium borohydride in 50 ml. of water. The reaction mixture was stirred for a period of 26 hours at room temperature, after which time 10 ml. of 2 N sulfuric acid was added, and the aqueous solution was extracted with two 50 ml. portions of ether. The ether was evaporated over a steam cone, leaving a residue consisting of high-boiling liquid and white crystals. The two were separated by vacuum filtration, and the white solid was identified as benzamide. The infrared spectrum of the liquid indicated that it was impure benzyl alcohol. The yields were 36% and 67% (crude), respectively.

Clemmensen Reduction. Zinc metal (4 g.), 0.4 g. of mercurous chloride, 1 ml. of concentrated hydrochloric acid, and 2.7 g. of N-acetyldibenzamide were added to 150 ml. of tetrahydrofuran in a 300 ml. round-bottomed flask. The flask was fitted with a Friedrich

cold-water condenser, and the mixture was refluxed for 3 hours. It was then extracted with two 150-ml. portions of anhydrous ether; aqueous sodium hydroxide was added to the aqueous phase, and the ether layer which appeared was separated. The combined ether portions were evaporated on a steam cone to a small volume, leaving a light-brown oil. The oil was boiled with petroleum ether (60-68°) in an attempt to induce crystallization, but no solid appeared. The mixture was allowed to evaporate slowly, and a small amount of crystals were formed. The solid was identified as benzamide. The yield was 0.11 g., 9%. No other product could be isolated.

SUMMARY

In attempts to synthesize unreported tertiary amides, benzoylpyridinium chloride was reacted with primary and secondary amides, in both ether and chloroform, and at different temperatures. These operations met with little success. Methacryloylpyridinium chloride was also prepared, but it was not found to be a good diacylating agent. It was observed that the use of chloroform as the solvent in low-temperature diacylation reactions of primary amides by benzoylpyridinium chloride is a necessity for the success of the reaction.

A study was made of some reactions of N-acetyldibenzamide as a representative of mixed aliphatic-aromatic tertiary amides. The results were those expected from previous work done in this laboratory, and it was observed that the acetyl group is the more labile, compared to the benzoyl group.

A major portion of this investigation was directed toward the determination of the structure of tertiary amides and related compounds. Spectral data and most of the chemical evidence obtained in this investigation supported the pyramidal structure assigned to tertiary amides. Some chemical evidence, such as the inability of quaternize tertiary amides, did not support the pyramidal structure; however, it is conceivable that quaternization might be made to occur if different reaction conditions or different quaternizing reagents are used.

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VITA

Martha Jane Gilleland, daughter of Mr. and Mrs. L.C. Martin, was born in Monroe, Louisiana, on September 9, 1940. She attended public elementary schools and graduated from Neville High School, in Monroe, in 1958.

In the fall of 1958, she entered Louisiana Polytechnic Institute, at Ruston, where she was active as an Honor Freshman, dormitory president, member of the Associated Women Students Governing Board, and member of Mortar Board. In June, 1962, she received her B.S. degree in chemistry, minoring in mathematics and physics.

Miss Gilleland entered the Graduate School of L.S.U. in February of 1963, and accepted a graduate teaching assistantship in chemistry. While at L.S.U., she served on the Graduate Student Council and was a member of Iota Sigma Pi honorary chemical society for women.

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EXAMINATION AND THESIS REPORT

Candidate: Martha Jane Gilleland

Major Field: Chemistry

Title of Thesis: I. An Investigation of the Acid-Catalyzed Alpha-Pyridilic Acid Rearrangement II. Chemistry of Mixed Aliphatic-Aromatic Tertiary Amides

Approved:

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Date of Examination:

January 8, 1968